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Die Arbeitslast-indexierte Analytik der Blutdruckregulation – Einfluss der vaskulären Funktion und Implikationen für die klinische Beurteilung von Leistungssportlern

Habilitationsschrift

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INHALTSVERZEICHNIS

ABKÜRZUNGSVERZEICHNIS

25-OH-Vitamin D	25-Hydroxy-Vitamin D
Aix	Augmentationsindex
Aix@75	Augmentationsindex auf eine Herzfrequenz von 75 standardisiert
BMI	Body-Mass-Index
cm	Zentimeter
cBP	central blood pressure (zentraler Blutdruck)
d	day (Tag)
DBP	diastolic blood pressure (diastolischer Blutdruck)
EKG	Elektrokardiogramm
ESC	European Society of Cardiology (Europäische Gesellschaft für Kardiologie)
g	Gramm
kcal	Kilokalorie
kg	Kilogramm
KOF	Körperoberfläche
m	Meter
m^2	Quadratmeter
MET	Metabolisches Äquivalent
min	Minute
ml	Milliliter
ng	Nanogramm
peak SBP/W-ratio	Quotient aus maximal erreichtem systolischen Blutdruckwert und maximal erreichter Wattzahl
PP	pulse pressure (Pulsdruck)
PWV	pulse wave velocity (Pulswellengeschwindigkeit)
s	Sekunde
SBP	systolic blood pressure (systolischer Blutdruck)
SBP/MET-slope	(Systolischer Blutdruck bei maximaler Belastung – systolischer Blutdruck in Ruhe)/(Metabolische Äquivalente bei maximaler Belastung – metabolisches Äquivalent in Ruhe)

SBP/W-slope	(Maximaler systolischer Blutdruck – erster systolischer Blutdruckwert unter Belastung)/(Maximal erreiche Wattzahl – erste absolvierte Wattzahl des Testes)
W	Watt
WADA	World Anti-Doping Agency (Welt-Anti-Doping-Agentur)
VO2 max.	Maximale Sauerstoffaufnahme

Die vorliegende kumulative Habilitationsschrift basiert auf folgenden Publikationen:

1. Bauer P, Henni S, Dörr O, Bauer T, Hamm CW, Most A. High prevalence of vitamin D insufficiency in professional handball athletes. Phys Sportsmed. 2019 Feb;47(1):71-77. doi: 10.1080/00913847.2018.1520055. Epub 2018 Sep 20. PMID: 30196746.
2. Bauer P, Kraushaar L, Hölscher S, Tajmiri-Gondai S, Dörr O, Nef H, Hamm C, Most A. Elite athletes as research model: vitamin D insufficiency associates with elevated central blood pressure in professional handball athletes. Eur J Appl Physiol. 2019 Oct;119(10):2265-2274. doi: 10.1007/s00421-019-04210-w. Epub 2019 Aug 19. PMID: 31428859.
3. Bauer P, Kraushaar L, Dörr O, Bauer T, Nef H, Hamm CW, Most A. Association of 25-hydroxy vitamin D level with the blood pressure response to a maximum exercise test among professional indoor athletes. Eur J Appl Physiol. 2020 Aug;120(8):1931-1941. doi: 10.1007/s00421-020-04421-6. Epub 2020 Jun 25. PMID: 32588193; PMCID: PMC7340632.
4. Bauer P, Kraushaar L, Most A, Hölscher S, Tajmiri-Gondai S, Dörr O, Troidl C, Bauer T, Nef H, Hamm CW, Keller T. Impact of Vascular Function on Maximum Power Output in Elite Handball Athletes. Res Q Exerc Sport. 2019 Dec;90(4):600-608. doi: 10.1080/02701367.2019.1639602. Epub 2019 Aug 9. PMID: 31397640.
5. Bauer P, Kraushaar L, Dörr O, Nef H, Hamm CW, Most A. Workload-indexed blood pressure response to a maximum exercise test among professional indoor athletes. Eur J Prev Cardiol. 2020 May 6:2047487320922043. doi: 10.1177/2047487320922043. Epub ahead of print. PMID: 32375548.
6. Bauer P, Kraushaar L, Hoelscher S, Weber R, Akdogan E, Keranov S, Dörr O, Nef H, Hamm CW, Most A. Blood Pressure Response and Vascular Function of Professional Athletes and Controls. Sports Med Int Open. 2021 Apr 19;5(2):E45-E52. doi: 10.1055/a-1400-1897. PMID: 33889714; PMCID: PMC8055378.
7. Bauer P, Kraushaar L, Dörr O, Nef H, Hamm CW, Most A. Sex differences in workload-indexed blood pressure response and vascular function among professional athletes and their utility for clinical exercise testing. Eur J Appl Physiol. 2021 Jul;121(7):1859-1869. doi: 10.1007/s00421-021-04656-x. Epub 2021 Mar 12. PMID: 33709207; PMCID: PMC8192366.

1. Einleitung

1.1 Arterielle Hypertonie bei Leistungssportlern

Die arterielle Hypertonie wurde als weltweit wichtigster Risikofaktor für kardiovaskuläre Erkrankungen und für ein vorzeitiges Sterben[1] identifiziert. Als arterielle Hypertonie wurde in den letzten Leitlinien der Europäischen Gesellschaft für Kardiologie (ESC) aus dem Jahr 2018 eine Erhöhung des systolischen Blutdruckes ≥ 140 mmHg und/oder eine Erhöhung des diastolischen Blutdruckes ≥ 90 mmHg definiert[2]. In Deutschland gelten aktuell ca. 30 % der Bevölkerung als Hypertoniker[3]. In der Altersgruppe der 20–29-jährigen Männer wird eine Prävalenz der arteriellen Hypertonie von 8,5 % angegeben, bei Männern im Alter von 30–44 Jahren lag diese bei 15,8 %[3-5]. Frauen weisen eine geringere Prävalenz von 1,3 % im Alter von 20–29 Jahren und 7,3 % im Alter von 30–44 Jahren auf[3].

Bei der Entstehung der arteriellen Hypertonie sind neben einer genetischen Prädisposition überwiegend Lebensstilfaktoren als ursächlich anzusehen[2]. Da eine arterielle Hypertonie in der Regel symptomlos verläuft und sich erst im Laufe der Jahre über die durch die Hypertonie bedingten Organschäden und Komplikationen klinisch bemerkbar macht, kommt der frühzeitigen Erkennung und adäquaten Behandlung eine entscheidende Bedeutung zu[2].

Regelmäßiges Ausdauertraining in einem moderaten Intensitätsbereich wirkt der Entstehung einer arteriellen Hypertonie entgegen und stellt zudem eine wirksame Therapieform dar[2, 6]. Folgerichtig findet sich bei Athleten eine deutlich geringere Prävalenz (3 %) der arteriellen Hypertonie als in der Normalbevölkerung[4, 5]. Neben der regelmäßig ausgeübten körperlichen Aktivität wird dies auf ein besseres Gesundheitsverhalten und eine geringere Exposition gegenüber traditionellen kardiovaskulären Risikofaktoren zurückgeführt.

Trotzdem stellt die arterielle Hypertonie die häufigste diagnostizierte kardiovaskuläre Erkrankung bei Leistungssportlern dar[5]. Die zugrundeliegenden Ursachen sind bisher nicht vollständig geklärt. Allerdings wird angenommen, dass erhöhter psychischer Stress infolge des regelmäßigen sportlichen Wettbewerbes auf höchstem Niveau sowie die hohen Trainingsvolumina und -intensitäten eine wesentliche Rolle spielen[4]. Zudem können auch bei Leistungssportlern die klassischen kardiovaskulären Risikofaktoren wie Dyslipoproteinämie (32 %), erhöhter Taillenumfang (25 %), familiäre Prädisposition (18 %) und Rauchen (8 %) in überraschend hoher Häufigkeit festgestellt werden[7].

Kontrovers wird derzeit diskutiert, inwieweit die ausgeübte Sportart einen Einfluss auf die Entstehung einer arteriellen Hypertonie hat. Einerseits wiesen Kraftsportler höhere Blutdruckwerte als Ausdauerathleten auf[4], andererseits wurde kein signifikanter Zusammenhang zwischen der ausgeübten Sportart und einer arteriellen Hypertonie gefunden[5]. Einigkeit besteht bisher dahingehend, dass Männer sowie Leistungssportler mit einer familiären Prädisposition für eine arterielle Hypertonie, mit einem höheren Body-Mass-Index (BMI) oder einer höheren Fettmasse ein höheres Risiko für die Entwicklung einer arteriellen Hypertonie aufweisen[5, 7].

Die Diagnosestellung der arteriellen Hypertonie und die diagnostische Vorgehensweise bei bestätigter arterieller Hypertonie unterscheiden sich nicht zwischen Leistungssportlern und der Normalbevölkerung[2, 6]. Allerdings absolvieren Leistungssportler in Deutschland regelmäßig eine vorgeschriebene Sporttauglichkeitsuntersuchung, bei der die Blutdruckmessung in Ruhe an beiden Armen ein fester Bestandteil ist[6]. Dadurch besteht die Chance, bei Athleten eine arterielle Hypertonie frühzeitig zu diagnostizieren, sie einer adäquaten Therapie zuzuführen und somit das kardiovaskuläre Risiko zu senken.

Die Therapie der arteriellen Hypertonie besteht aus nichtmedikamentösen und medikamentösen Maßnahmen und orientiert sich am kardiovaskulären Risiko des Patienten[2]. Dies gilt auch für Leistungssportler[6].
Die nichtmedikamentösen Therapiemaßnahmen stellen hierbei die Basis der Therapie dar. Sie bestehen aus regelmäßiger körperlicher Aktivität mit moderater Intensität im Umfang von 150 Minuten pro Woche beziehungsweise 75 Minuten pro Woche bei intensiver Aktivität, Normalisierung des Körpergewichtes bei Übergewichtigen, Einschränkung des Salzkonsums auf 3–5 g/d, Rauchverzicht, Einschränkung des Alkoholkonsums und eine mediterrane Ernährungsweise[2]. Zudem wird ein Krafttraining, welches 3–4-mal pro Woche mit moderater Intensität im Kraftausdauerbereich durchgeführt werden sollte, zur Senkung des Blutdruckes empfohlen[6]. Zu beachten ist hierbei jedoch, dass Krafttraining nur bei einer kontrollierten arteriellen Hypertonie, definiert als systolischer Blutdruck < 160 mmHg, zum Einsatz kommen sollte[6].

Bei der medikamentösen Therapie von Leistungssportlern müssen einige Besonderheiten beachtet werden. So führt eine Therapie mit Betablockern zu einer Reduktion der maximalen Herzfrequenz, was sich negativ auf die Leistungsfähigkeit auswirkt. Ferner sind Betablocker

in Geschicklichkeitssportarten als Dopingmittel indexiert. Diuretika sind bei allen Leistungssportlern als nicht erlaubte Substanzen von der Welt-Anti-Doping-Agentur (WADA) gekennzeichnet, weil sie missbräuchlich zur Verschleierung anderer Dopingvergehen eingesetzt werden[6].

Athleten mit unkontrollierter arterieller Hypertonie dürfen so lange keinen Wettkampfsport ausüben (Ausnahme: Geschicklichkeitssportarten), bis die arterielle Hypertonie kontrolliert ist. Hingegen ist bei einer gut kontrollierten arteriellen Hypertonie, auch wenn bereits Endorganschäden vorliegen oder ein hohes kardiovaskuläres Risikoprofil besteht, eine Wettkampfteilnahme bei den meisten Sportarten erlaubt. Lediglich hochintensive, kraftbasierte Wettkampfsportarten wie Diskuswerfen, Kugelstoßen, Speerwerfen und Gewichtheben sollten nicht ausgeübt werden[6]. Diese Empfehlung beruht auf der Beobachtung, dass insbesondere isometrisch durchgeführtes Krafttraining und das Valsalva-Manöver zu erheblichen Anstiegen des systolischen und diastolischen Blutdruckes führen[6] und damit das Risiko für ein kardiovaskuläres Ereignis bei diesen Patienten erhöhen.

1.2 Blutdruckregulation unter Belastung

Bei steigender Belastung kommt es zu einem Anstieg des systolischen Blutdruckes, wohingegen der diastolische Blutdruck unter Belastung nur wenig ansteigt. Dies liegt vor allem an der Steigerung des Herzzeitvolumens, um den bei der verstärkten Muskelarbeit anfallenden Sauerstoffbedarf zu decken. Gleichzeitig kommt es zu einer funktionellen Sympathicolyse mit Verringerung des Gefäßwiderstandes in der arbeitenden Skelettmuskulatur und einer Erhöhung des Gefäßwiderstandes im Splanchnikusgebiet, der Nieren und der Leber. Die Steigerung des Herzzeitvolumens ist hierbei physiologisch stärker ausgeprägt als die Reduktion des vaskulären Widerstandes, woraus eine Erhöhung des mittleren arteriellen Druckes infolge der Erhöhung des systolischen Blutdruckes resultiert. Daraus wird ersichtlich, dass die Blutdruckregulation unter Belastung sowohl von der kardialen als auch der vaskulären Funktion bestimmt wird.

Im klinischen Alltag werden Belastungsuntersuchungen vorwiegend in Form eines Belastungs-EKGs mit oder ohne gleichzeitiger Atemgasanalyse durchgeführt, um kardiovaskuläre Pathologien, die in Ruhe verborgen bleiben würden, zu detektieren und um die körperliche Leistungsfähigkeit des Patienten zu bestimmen. Bei Wettkampfathleten wird ein solcher maximaler Ausbelastungstest als Bestandteil der Sporttauglichkeitsuntersuchung empfohlen[6].

Daher erscheint eine klare Einordnung, wann eine normale Blutdruckantwort beim Ausbelastungstest vorliegt und wann nicht, von entscheidender Bedeutung. Umso erstaunlicher ist es, dass die aktuell gültigen Leitlinien der arteriellen Hypertonie[2] explizit das Fehlen einer allgemein akzeptierten Definition der normalen Blutdruckantwort bemängeln. Dies ist auf die sehr widersprüchlichen Ergebnisse von Studien zurückzuführen, die den prognostischen Wert der Blutdruckantwort auf eine definierte Belastung und deren Einfluss auf das kardiovaskuläre Risiko untersucht haben. So wiesen einige Studien auf ein erhöhtes kardiovaskuläres Risiko bei niedrigen systolischen Blutdruckwerten bei maximaler Belastung hin[8], wohingegen andere Studien höhere erreichte systolische Blutdruckwerte bei Maximalbelastung einerseits mit einem reduzierten[9], andererseits mit einem erhöhten kardiovaskulären Risiko in Verbindung brachten[10].

Diese Unklarheit bezüglich eines normalen Blutdruckverhaltens unter Belastung stellt insbesondere bei der Evaluation von Athleten im Rahmen der Sporttauglichkeitsuntersuchung ein Problem dar. Aufgrund der physiologisch nahezu linearen Beziehung zwischen systolischem Blutdruck und steigender Arbeitslast werden insbesondere bei Individuen mit

hoher körperlicher Fitness höhere maximale Blutdruckwerte erreicht. Daher ist hier die Abgrenzung einer noch physiologischen von einer bereits pathologischen Blutdruckantwort deutlich erschwert. Zudem sind Athleten durch das Training und den Wettkampf in der Regel länger und häufiger einem höheren Blutdruck unter Belastung ausgesetzt.

In einer großen Kohorte von Olympiateilnehmern lag die 95-%-Perzentile des maximal erreichten systolischen Blutdruckes bei männlichen Athleten bei < 220 mmHg und bei weiblichen Athleten bei < 200 mmHg[11].

Die aktuellen sportkardiologischen Leitlinien[6] weisen darauf hin, dass bei normotensiven Athleten eine überschießende Blutdruckantwort (≥ 207 mmHg systolischer Blutdruck) unter Belastung das Risiko für das Auftreten einer arteriellen Hypertonie erhöht[12]. Dies wurde mit einer bereits bestehenden vaskulären Funktionseinschränkung bei diesen Athleten erklärt, welche mit den traditionellen Messmethoden noch nicht erfasst wurde. Die subklinische Einschränkung der vaskulären Funktion wird daher als Risikofaktor für die Entwicklung einer arteriellen Hypertonie angesehen.

Nichtsdestotrotz sind bis heute keine klaren Grenzen der normalen Blutdruckantwort bei Athleten definiert, was an der bisherigen Vorgehensweise der Orientierung an Absolutwerten liegt. Erstmalig findet sich nun jedoch in den europäischen Leitlinien[6] der Hinweis, dass bei einem systolischen Blutdruck > 200 mmHg bei 100 Watt Belastung die antihypertensive Therapie optimiert werden sollte, sofern bereits eine arterielle Hypertonie vorliegt. Bei normotensiven Blutdruckwerten im Ruhe sollte in diesem Falle eine weiterführende klinische Evaluation stattfinden, um eine arterielle Hypertonie und/oder andere kardiovaskuläre Pathologien auszuschließen[6]. Diese Neuerung, dass der erreichte systolische Blutdruckwert auf die jeweilige Belastung indexiert betrachtet wird, erscheint sinnvoll und hilft insbesondere bei der Beurteilung der belastungsinduzierten Blutdruckantwort von körperlich fitten Individuen. Hierauf aufbauend entwickelten Hedman und Kollegen[9] einen Index, der die systolische Blutdruckantwort bei einem Belastungstest auf das geleistete metabolische Äquivalent bezieht. Dieser Index wurde als SBP/MET-slope bezeichnet und wird über folgende Formel berechnet:

$$\frac{\text{Systolischer Blutdruck bei maximaler Belastung – systolischer Blutdruck in Ruhe}}{\text{Metabolisches Äquivalent bei maximaler Belastung – metabolisches Äquivalent in Ruhe}}$$

Das metabolische Äquivalent (MET) ist ein Maß für den Energieverbrauch des Menschen und spiegelt das Verhältnis von Arbeits- zu Ruheumsatz wider. Dabei wird 1 MET als das Maß

der Sauerstoffaufnahme einer erwachsenen Person im ruhigen Sitzen definiert und entspricht einer Sauerstoffaufnahme von 3,5 Milliliter (ml) pro Minute und Kilogramm (kg) Körpergewicht. Korrespondierend zur Sauerstoffaufnahme lässt sich daraus ein Kalorienumsatz in Ruhe (im Sitzen) von 1 Kilokalorie (kcal) pro Kilogramm (kg) Körpergewicht ableiten. Das Energieäquivalent von 1 MET beträgt demnach ca. 1 kcal pro kg und Stunde. Hierdurch kann auf einfache Weise der individuelle aktivitätsbedingte Energieverbrauch ermittelt werden.

In den amerikanischen sportmedizinischen Empfehlungen aus dem Jahr 2013[13] wurde bereits eine Steigerung des systolischen Blutdruckes um 10 mmHg pro geleisteter MET als Normwert definiert. Allerdings wurde der SBP/MET-slope erstmalig im Jahr 2019 systematisch in einer großen männlichen Patientenkohorte (n = 7542, Alter 58,6 ± 11 Jahre) untersucht und mit der Gesamtmortalität verglichen[9]. Nach einem Beobachtungszeitraum von 18,4 Jahren zeigte sich, dass ein SBP/MET-slope > 10 mmHg/MET mit einer um 20 % höheren Sterblichkeit assoziiert war (Hazard-Ratio 1,2 (1,10–1,31)). In der Untergruppe (n = 709) der Patienten mit einem niedrigen Ausgangsrisiko lagen der Mittelwert des SBP/MET-slope bei 4,9 mmHg/MET und die 95-%-Perzentile bei 10 mmHg/MET[9] und somit deutlich unterhalb der oben genannten Normwerte[13]. Zudem war der SBP/MET-slope den maximal erreichten systolischen Blutdruckwerten in der Vorhersage der Sterblichkeit überlegen, wobei ein höherer SBP/MET-slope mit einem höheren Sterblichkeitsrisiko verbunden war[9]. Interessanterweise war ein maximaler systolischer Blutdruck von > 210 mmHg, also oberhalb des in den vorhergehenden europäischen Leitlinien von 2013[14] definierten oberen Grenzwertes, mit einer geringeren Sterblichkeit assoziiert.

Diese Untersuchung zeigt somit erstmalig, dass die Arbeitslast-indexierte Betrachtungsweise der Blutdruckantwort unter Belastung eine höhere prognostische Relevanz hat als der maximal erreichte systolische Blutdruck.

Auf dieser Untersuchung aufbauend definierten Hedman und Kollegen[15] im Jahr 2020 alters- und geschlechtsspezifische Normwerte für eine Arbeitslast-indexierte Betrachtung der Blutdruckantwort bei einem Fahrradergometertest. Hierbei wurden insgesamt 12 976 Personen im Alter von 18–85 Jahren untersucht und Normwerte aus einer Kohorte von 3839 gesunden Teilnehmern ermittelt[15]. Zur Indexierung des systolischen Blutdruckanstieges in Relation zur Arbeitslast in Watt bei Durchführung der Fahrradergometrie führten die Autoren zwei weitere Parameter ein: zum einen den SBP/Watt-slope, der die Steilheit der systolischen Blutdruckantwort in Bezug zur Steigerung der Wattzahl widerspiegelt und folgendermaßen kalkuliert wird:

$$\frac{\text{Maximaler systolischer Blutdruck} - \text{erster systolischer Blutdruckwert unter Belastung}}{\text{Maximal erreiche Wattzahl} - \text{erste absolvierte Wattzahl des Testes}}$$

Zum anderen wurde die sogenannte peak SBP/Watt-ratio als Quotient aus maximal erreichtem systolischen Blutdruckwert und maximal erreichter Wattzahl errechnet.

Während die maximal erreichten systolischen Blutdruckwerte bei Männern (202 ± 22 mmHg) höher waren als bei Frauen (188 ± 24 mmHg), war der SBP/W-slope bei den Frauen (0,52 ± 0,21 mmHg/W) um 27 % steiler als bei den Männern (0,41 ± 0,15 mmHg/W), was auf relevante geschlechtsspezifische Unterschiede in der Blutdruckregulation unter Belastung hindeutet[15]. Neben diesen geschlechtsspezifischen Unterschieden beobachteten die Autoren eine positive signifikante Korrelation zwischen Alter und Arbeitslast-indexierter Blutdruckantwort.

Die Autoren interpretierten ihre Ergebnisse als Hinweis auf geschlechtsabhängige Unterschiede in der zentralen Hämodynamik und der vaskulären Funktion[15].

Die in dieser Studie erstmalig präsentierten geschlechtsspezifischen Referenzwerte der belastungsindexierten Blutdruckantwort unterstreichen die Notwendigkeit einer nach Alter, Geschlecht und Arbeitslast zu differenzierenden Beurteilung der Blutdruckantwort.

1.3 Zentrale Hämodynamik und vaskuläre Funktion

Die Höhe des Blutdruckes wird prinzipiell durch das Zusammenspiel aus Herzminutenvolumen und Gefäßfunktion determiniert. Während in früheren Jahrzehnten unter „Gefäßfunktion“ meist nur der periphere Widerstand subsumiert wurde, hat sich in den letzten Jahren eine differenzierte Betrachtungsweise der Gefäßfunktionen etabliert, welche die pulsatilen Elemente des Blutdruckes miteinbezieht. Dabei muss berücksichtigt werden, dass die komplexen hämodynamischen Vorgänge im Gefäßsystem dynamisch sind und sich in den verschiedenen Gefäßregionen zum Teil erheblich voneinander unterscheiden. Zur Beurteilung der Gefäßfunktion müssen daher mehrere Parameter herangezogen werden, die die physikalischen Eigenschaften der Arterien adäquat beschreiben und messbar machen.

Die systolische linksventrikuläre Kontraktion bewirkt den Transport der Blutsäule (Flusswelle) und startet zugleich eine Druckwelle, die sich entlang des arteriellen Gefäßbaumes ausbreitet und als Pulswellengeschwindigkeit (PWV) bezeichnet wird. An den Verzweigungen der Arterien wird diese Welle reflektiert und wieder nach zentral propagiert, wodurch es zu einer Addition mit der initialen Pulswelle kommt. Diese erreicht bei Gesunden die aszendierende Aorta in der Diastole desselben Herzzyklus, also nach dem Aortenklappenschluss, und führt so zu einer Erhöhung des diastolischen Blutdruckes und damit der Koronarperfusion *(Abbildung 1)*. Eine Einschränkung der Dämpfungsfunktion der Aorta infolge eines Verlustes der Elastizität führt zu einer verfrühten Pulswellenreflexion und zu einer erhöhten PWV. Dann erreicht die reflektierte Pulswelle die aszendierende Aorta entsprechend früher, was eine erhöhte kardiale Nachlast und aortale Wandspannung zur Folge hat. Ferner kommt es dann zu einer Reduktion der diastolischen Druckwelle und damit der Koronarperfusion *(Abbildung 2)*.

Die aortale PWV ist heute als Maß für die Gefäßsteifigkeit anerkannt und besitzt eine unabhängige prognostische Bedeutung[16, 17]. Bei einer Zunahme der arteriellen Gefäßsteifigkeit und damit der PWV kommt es zu einer Zunahme des systolischen Blutdruckes und des Pulsdruckes (PP). Dies steigert das Risiko für die Entwicklung einer arteriellen Hypertonie[18].

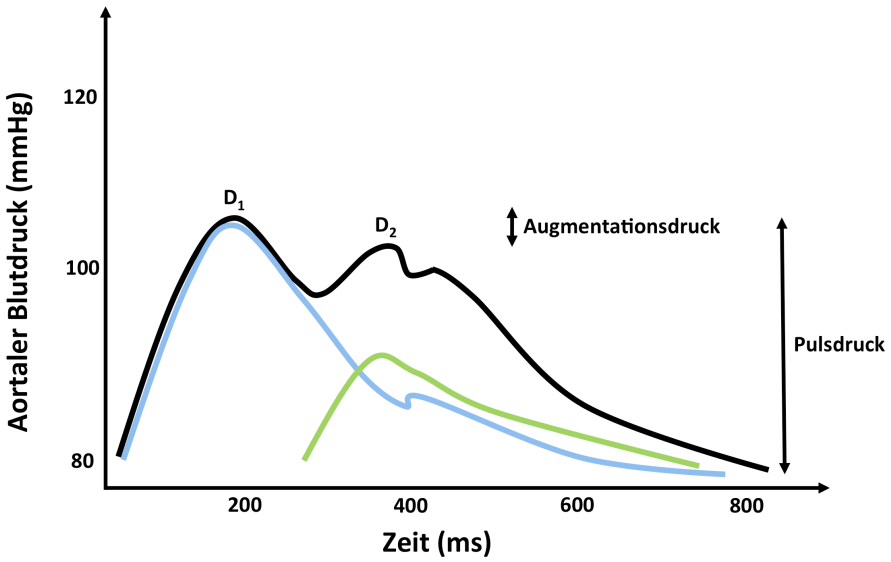

Abb. 1: Schematische Darstellung der aortalen Pulsdruckkurve bei normaler Gefäßsteifigkeit

D1: erste Druckspitze, ausgelöst durch die linksventrikuläre Kontraktion.

D2: zweite Druckspitze, bedingt durch die Addition der antegraden und reflektierten Pulswelle.

Blaue Linie: antegrade Pulswelle, grüne Linie: reflektierte Pulswelle.

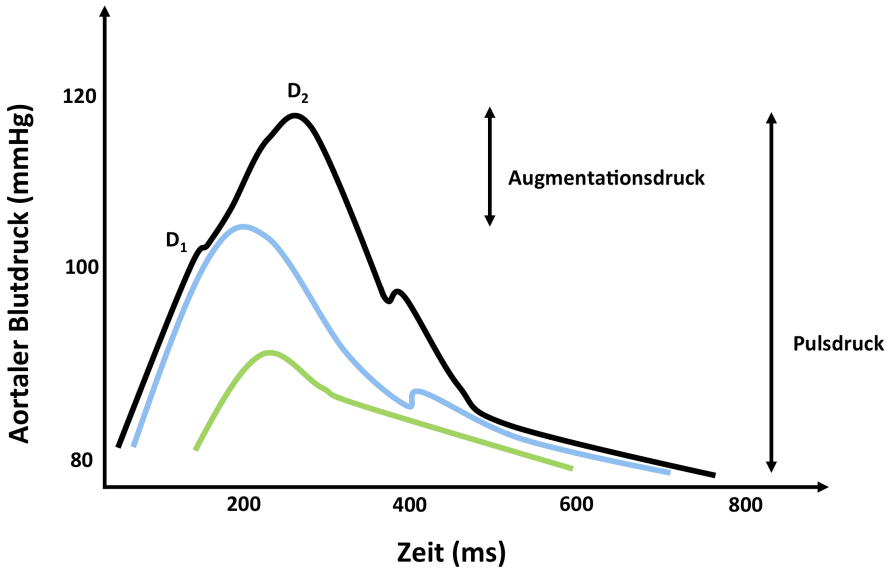

Abb. 2: Schematische Darstellung der aortalen Pulsdruckkurve bei erhöhter Gefäßsteifigkeit

D1: erste Druckspitze, ausgelöst durch die linksventrikuläre Kontraktion.

D2: zweite erhöhte Druckspitze, bedingt durch die früher einfallende reflektierte Pulswelle.

Hierdurch kommt es zum erhöhten Pulsdruck und zu einem positiven Augmentationsdruck.

Blaue Linie: antegrade Pulswelle, grüne Linie: reflektierte Pulswelle.

Es besteht allerdings eine große Diskrepanz zwischen den durch eine erhöhte arterielle Steifigkeit ausgelösten starken Veränderungen der zentralen Hämodynamik und den über eine brachiale Blutdruckmessung erkennbaren geringen Veränderungen der peripheren Blutdruckwerte[19].

Der aortale (zentrale) systolische Blutdruck wirkt auf Herz und Gehirn und determiniert die kardiale Nachlast. Daher hat er eine wichtigere prognostische Bedeutung als der periphere Blutdruck[19, 20] und ist stärker mit dem Auftreten von hypertoniebedingten Organschäden[21] sowie kardiovaskulären Ereignissen assoziiert[22-24]. Kürzlich wurden alters- und geschlechtsspezifische Normwerte für den zentralen Blutdruck publiziert[25].

Die durch die reflektierte Pulswelle induzierte Drucksteigerung des systolischen zentralen Blutdruckes (cBP) wird als Augmentationsdruck bezeichnet. Der Anteil des Augmentationsdruckes am Pulsdruck wird als Augmentationsindex (Aix) berechnet. Da der Augmentationsindex von der Herzfrequenz abhängig ist, hat sich dessen Standardisierung auf eine Herzfrequenz von 75/min etabliert (Aix@75). Ferner wird der Augmentationsindex von funktionellen Veränderungen der peripheren Gefäße wie Vasokonstriktion, Vasodilatation und Änderungen der Endothelfunktion beeinflusst. Der Augmentationsindex ergänzt somit die PWV als Parameter zur Erfassung der arteriellen Gefäßsteifigkeit.

Eine steigende arterielle Steifigkeit führt infolge des steigenden Pulsdruckes zu erheblichen Veränderungen der Mikrozirkulation und des peripher-vaskulären Widerstandes. So kommt es zu pulsatilen Strömungen in Gefäßregionen, die physiologisch eine laminäre Strömung aufweisen. Die Konsequenz sind Organschäden, die wiederum als Folge des nunmehr erhöhten peripher-vaskulären Widerstandes eine Erhöhung der arteriellen Steifigkeit bewirken.

Zusammenfassend ermöglicht demnach die Messung der zentralen Hämodynamik und der Gefäßsteifigkeit eine frühzeitige Erkennung kardiovaskulärer Funktionseinschränkungen. Die Determinanten der Funktionsanalyse sind der zentrale Blutdruck, der zentrale Pulsdruck, die Pulswellengeschwindigkeit, der Augmentationsindex@75 sowie der peripher-vaskuläre Widerstand. Bei der arteriellen Hypertonie liefern die Messungen dieser physikalischen Eigenschaften der Gefäße zusätzliche Informationen im Vergleich zur alleinigen Messung des brachialen Blutdruckes und imponieren daher als sensitivere Parameter zur Detektion vaskulärer Funktionseinschränkungen. Dies spiegelt sich in den aktuellen Hypertonie-Leitlinien der ESC wider, in denen ein Pulsdruck von ≥ 60 mmHg sowie eine Pulswellengeschwindigkeit > 10 m/s als hypertoniebedingte Organschäden anerkannt werden[2].

Heutzutage ist es möglich, die physikalischen Gefäßparameter einfach nichtinvasiv über eine Pulswellenanalytik zu messen und damit für den klinischen Alltag zugänglich zu machen. Während die früher als Goldstandard verwendete Applanationstonometrie aufgrund der Messmethodik fehleranfällig ist und daher nur eingeschränkt reproduzierbare Ergebnisse liefern kann, sind kürzlich oszillometrische Verfahren entwickelt worden, die untersucherunabhängige Ergebnisse generieren[26]. Zudem wurden verschiedene Geräte in Studien klinisch validiert[26, 27]. Das in der hier vorliegenden Habilitationsschrift benutzte oszillometrische Verfahren wurde gegenüber einer invasiven Goldstandardmessung des zentralen Blutdruckes validiert[28]. Zudem liegt der hierbei benutzten validierten Transferfunktion das aktuellste elektronische Modell des menschlichen Gefäßsystems zugrunde, welches genetische Algorithmen zur Optimierung der Genauigkeit der Replikation von Pulsdruckkurven verwendet[29].

Bei Leistungssportlern gibt es gegenwärtig uneinheitliche Studienergebnisse zur Auswirkung der intensiven sportlichen Aktivität auf die arterielle Gefäßsteifigkeit und den zentralen Blutdruck. Zum einen werden eine erhöhte arterielle Steifigkeit[30-32] und ein erhöhter zentraler Blutdruck[30] bei Athleten beschrieben, andererseits wurden genau gegenteilige Effekte[33-35] oder keine Effekte[36] beobachtet. Inwieweit die Art der ausgeübten sportlichen Aktivität die arterielle Gefäßsteifigkeit beeinflusst, ist zudem noch Gegenstand von Studien[37].
Bei Leistungssportlern können selbst leichtgradige kardiovaskuläre Funktionseinschränkungen die Leistungsfähigkeit vermindern und langfristig mit schwerwiegenden gesundheitlichen Folgen verbunden sein. Die vaskuläre Funktionsanalyse mittels validierter oszillometrischer Verfahren könnte daher zur frühzeitigen Detektion einer vaskulären Funktionseinschränkung genutzt werden. Die bei kompetitiven Athleten vorgeschriebene Sporttauglichkeitsuntersuchung bietet hierfür eine günstige Gelegenheit.
In einer kürzlich veröffentlichten Studie mit gesunden jungen Teilnehmern beider Geschlechter (Alter 37 ± 5 Jahre) konnte zudem gezeigt werden, dass die in Ruhe gemessene PWV mit einer überschießenden Blutdruckantwort assoziiert ist und diese voraussagen kann[38]. Selbst bei in Ruhe normotensiven Menschen kann es unter Belastung zu einer überschießenden Blutdruckregulation kommen[39], die auf eine subklinische vaskuläre Funktionseinschränkung zurückzuführen ist. Die vaskuläre Funktionsanalyse kann somit dazu beitragen, eine bessere kardiovaskuläre Risikoeinschätzung insbesondere bei jungen und ansonsten gesunden Menschen zu erreichen[39, 40].

1.4 Leistungssportler in der kardiovaskulären Forschung

Leistungssportler stellen ein besonderes Studienkollektiv dar. Sie sind zumeist jünger, gesund und nehmen häufig keine Medikamente ein. Ferner weisen sie durch das regelmäßige und intensive Training sowie die regelmäßigen Wettkämpfe eine hohe kardiopulmonale Leistungsfähigkeit auf, welche die der Normalbevölkerung und der Hobbysportler der gleichen Sportart übersteigt[41, 42]. Insbesondere in den in Deutschland populären Mannschaftssportarten wie Fußball, Handball, Eishockey und Basketball ist die interindividuelle Variabilität der kardiopulmonalen Leistungsfähigkeit zwischen den Spielern eines professionellen Teams mit Ausnahme der Torhüter gering.

Die körperliche Fitness und Leistungsfähigkeit spielen eine herausragende Rolle zur Prävention und Therapie kardiovaskulärer Erkrankungen[43, 44]. Zudem wirkt regelmäßiges Training mit mäßiger Intensität blutdrucksenkend[6] und muss daher in Studien, die den Einfluss einzelner Faktoren auf den Blutdruck untersuchen, als wichtige Komponente berücksichtigt werden. Eine Studienpopulation von Leistungssportlern kann daher zu Erkenntnissen führen, die in Normalpopulationen mit ihrem typischerweise breiten Spektrum der körperlichen Aktivität und Fitness nicht erreichbar wären.

Deshalb bietet sich gerade in dieser Kohorte die Möglichkeit, die Korrelation zwischen Hämodynamik, Blutdruckregulation und Leistungsfähigkeit unter Einbeziehung einer weiteren Variable zu beleuchten. Wir untersuchten daher in unseren Arbeiten den Einfluss von Vitamin D auf die Blutdruckregulation und kardiovaskuläre Funktion bei Leistungssportlern.

Anlass dazu war die bisher widersprüchliche Studienlage zum Einfluss von Vitamin D auf den Blutdruck und die kardiovaskuläre Funktion in nichtathletischen Studienpopulationen[45-47] sowie auf die Leistungsfähigkeit bei Athleten[48, 49]. Wir gingen davon aus, selbst geringe durch einen Vitamin-D-Mangel induzierte Änderungen der kardiovaskulären Funktion bei Leistungssportlern feststellen zu können. Zudem ist ein Vitamin-D-Mangel auch bei Leistungssportlern weit verbreitet[48, 49].

2. Fragestellung und Zielsetzung der Arbeit

Die vorliegende Habilitationsschrift beschäftigt sich mit der Fragestellung, welchen Einfluss die zentrale Hämodynamik und die vaskuläre Funktion auf die Blutdruckregulation und Leistungsfähigkeit bei Leistungssportlern haben.
Durch das neugewonnene Instrument der validierten, nichtinvasiven Analyse der physikalischen Gefäßeigenschaften mittels der Pulswellenanalytik ergab sich die Möglichkeit der differenzierten kardiovaskulären Funktionsanalyse, um frühzeitig eine vaskuläre Funktionsstörung bei den Athleten zu erkennen.
Durch das homogene und gesunde Studienkollektiv der Leistungssportler war es zudem möglich, potenzielle Zusammenhänge zwischen 25-OH-Vitamin D und der Blutdruckregulation unabhängig von der kardiopulmonalen Fitness zu untersuchen.

Mit der Einführung der Arbeitslast-indexierten Betrachtungsweise der Blutdruckantwort bei Athleten wollten wir außerdem spezifische Unterschiede der Blutdruckantwort zwischen Leistungssportlern und Nichtathleten untersuchen. Das Ziel hierbei war es, Referenzwerte für die einzelnen neuen Parameter der Arbeitslast-indexierten Blutdruckantwort zu generieren, um eine klinische Beurteilung der Blutdruckantwort bei männlichen und weiblichen Leistungssportlern während der Sporttauglichkeitsuntersuchung vornehmen zu können. Damit adressierten wir die bisher ungelöste, allerdings sehr wichtige Frage danach, wie die Blutdruckantwort während eines Ausbelastungstestes bei Athleten zu beurteilen ist. Inwieweit durch eine vaskuläre Funktionsanalyse in Ruhe prädiktive Aussagen über die spezifische Blutdruckregulation unter Belastung und die Leistungsfähigkeit bei Leistungssportlern getroffen werden können, war ferner Gegenstand dieser Untersuchung.

3. Einfluss von 25-OH-Vitamin D auf die Blutdruckregulation bei Leistungssportlern

3.1 Prävalenz eines 25-OH-Vitamin-D-Mangels bei professionellen Handballspielern

Vitamin D ist ein fettlösliches Hormon, welches für den Knochenstoffwechsel und die Immunfunktionen von herausragender Bedeutung ist[50, 51]. Zudem wurden Vitamin-D-Rezeptoren in vielen verschiedenen Regionen des menschlichen Körpers gefunden[51], was auf zusätzliche Wirkungen von Vitamin D im menschlichen Körper hinweist[48]. So zeigten sich unerwartete Assoziationen zwischen einem Vitamin-D-Mangel und verschiedenen kardiovaskulären Erkrankungen[48, 51-55].

Die Auswirkungen eines Vitamin-D-Mangels auf die sportliche Leistungsfähigkeit und Verletzungshäufigkeit wurden in der Sportmedizin intensiv untersucht[56]. Bisherige Untersuchungen weisen darauf hin, dass ein Vitamin-D-Mangel zu einer eingeschränkten Leistungsfähigkeit bei Athleten führt[48], was anhand der muskuloskelettalen[57, 58] und kardiovaskulären Effekte [56] von Vitamin D erklärt wurde.

Die anzustrebenden optimalen Vitamin-D-Spiegel sowohl für die Normalbevölkerung als auch für Athleten sind derzeit wissenschaftlich umstritten[48, 54, 58-61] und es existieren zudem unterschiedliche Definitionen eines Vitamin-D-Mangels[48, 59]. Da Konzentrationen ≥ 30 ng/ml 25-OH-Vitamin D das Risiko für Knochenmineralisationsdefekte minimieren[62], definierten wir in unseren Studien, wie auch andere Arbeitsgruppen[63, 64], 25-OH-Vitamin-D-Spiegel < 30 ng/ml als insuffiziente Vitamin-D-Spiegel und somit als Vitamin-D-Mangel.

Als Risikofaktoren für einen Vitamin-D-Mangel bei Athleten wurden unter anderem geographische Faktoren (> 35 Grad nördlicher Breitengrad), eine schwarze Hautfarbe, ein höherer BMI, eine geringe körperliche Aktivität, eine geringe Sonneneinstrahlung sowie die Ausübung einer Hallensportart identifiziert[48, 65, 66]. Ein Vitamin-D-Mangel weist eine hohe Prävalenz in der Bevölkerung Deutschlands auf[66], auch bei Athleten[65].

Untersuchungen bezüglich der Häufigkeit eines Vitamin-D-Mangels bei professionellen Handballspielern in Deutschland gab es noch nicht. Daher war das Ziel der im Folgenden genannten ersten Publikation, die Prävalenz eines 25-OH-Vitamin-D-Mangels bei professionellen Handballspielern in Deutschland zu bestimmen.

Publikation Nr. 1:

Bauer P, Henni S, Dörr O, Bauer T, Hamm CW, Most A. High prevalence of vitamin D insufficiency in professional handball athletes. Phys Sportsmed. 2019 Feb;47(1):71-77. doi: 10.1080/00913847.2018.1520055. Epub 2018 Sep 20. PMID: 30196746.

In dieser Arbeit wurde der 25-OH-Vitamin-D-Status von insgesamt 70 professionellen männlichen Handballspielern kaukasischer Herkunft (Alter 26 ± 5 Jahre) evaluiert. Die Untersuchungen fanden im Rahmen einer Sporttauglichkeitsuntersuchung im Juli vor der Wettkampfsaison und nach einer sechswöchigen Wettkampfpause statt. Alle eingeschlossenen Athleten waren gesund, keine Solariumnutzer und nahmen keine Medikamente oder Nahrungsergänzungsmittel in Form von Vitaminsupplementen ein. Da die Sonneneinstrahlung die wichtigste natürliche Determinante der körpereigenen Vitamin-D-Produktion ist, wurde ein validierter Sonnenexpositionsfragebogen genutzt[67], um die Sonnenexposition der letzten zwei Wochen vor der Untersuchung zu bestimmen. Das Ergebnis des Fragebogens (über zwei Wochen) ist ein Punktwert von 0–112, wobei höhere Werte eine stärkere Sonnenexposition anzeigen. Ferner wurden die Parathormonwerte bestimmt, da bei einem 25-OH-Vitamin-D-Mangel reaktiv die Parathormonsekretion und damit die Osteoklastenaktivität ansteigen. Als insuffiziente 25-OH-Vitamin-D-Spiegel definierten wir Werte < 30 ng/ml, hingegen wurden Werte ≥ 30 ng/ml als suffiziente Spiegel angesehen[48, 68].

Obwohl die Untersuchungen im Juli stattfanden und zuvor eine wettkampffreie Zeit mit Sommerurlaub bestand, detektierten wir in 44,3 % (n = 31) der untersuchten Leistungssportler insuffiziente 25-OH-Vitamin-D-Werte (23,2 ± 5,4 ng/ml). Bei 39 Athleten (55,7 %) lagen die 25-OH-Vitamin-D-Spiegel im suffizienten Bereich (39,1 ± 8,7 ng/ml). Somit konnten wir eine hohe Prävalenz eines Vitamin-D-Mangels in unserer Kohorte feststellen, obwohl zum Zeitpunkt der Untersuchung im Sommer die höchsten Vitamin-D-Spiegel zu erwarten gewesen wären. Überraschenderweise zeigte sich jedoch zwischen den Leistungssportlern mit insuffizientem und denen mit suffizientem Vitamin-D-Spiegel kein signifikanter Unterschied im Sonnenexpositionspunktwert. In beiden Gruppen waren ähnlich hohe Punktwerte erreicht worden. Ferner waren keine signifikanten Unterschiede in Bezug auf Alter, Körpergröße, Gewicht, Body-Mass-Index oder Trainingshistorie zwischen den beiden Gruppen festzustellen.

Lediglich in der differenzierten Betrachtungsweise mit Vergleich der Athleten mit einem Spiegel ≥ 30 ng/ml mit denen, die einen 25-OH-Vitamin-D-Spiegel < 20 ng/ml aufwiesen

(n = 6), zeigten sich signifikante Unterschiede in der Sonnenexposition. Allerdings muss bei der Betrachtung dieser Ergebnisse berücksichtigt werden, dass der bei Kaukasiern validierte Sonnenexpositionsfragebogen den wichtigen Aspekt der Sonnenschutzcremes nicht erfasst. Dies stellt eine wichtige Limitation der Erhebungsmethode dar.
Allerdings konnten wir signifikante Unterschiede des Parathormonspiegels zwischen den Athleten mit suffizienten und denen mit insuffizienten 25-OH-Vitamin-D-Spiegeln aufzeigen. Dieses Ergebnis stützt die Schwelle von 30 ng/ml 25-OH-Vitamin D als unteren Grenzwert zur Erhaltung der Knochengesundheit, da eine Parathormonerhöhung eine gesteigerte Osteoklastenaktivität und somit eine unzureichende Vitamin-D-Wirkung am Knochen widerspiegelt. Dies spielt insbesondere für Leistungssportler eine große Rolle, da hier häufiger Stressfrakturen im Vergleich zur Normalpopulation beobachtet werden, was mit einer erhöhten mechanischen Beanspruchung erklärt wird. Zugleich werfen unsere Ergebnisse die Frage auf, wie in dieser Population effektiv einem Vitamin-D-Mangel vorgebeugt werden kann, um längere Ausfallzeiten zu verhindern.

Zusammenfassend ließ sich in unserer Studie bei professionellen männlichen Hallensportlern eine hohe Prävalenz eines Vitamin-D-Mangels selbst in den Sommermonaten detektieren. Daher wurden regelmäßige Kontrollen des Vitamin-D-Spiegels bei Leistungssportlern in den verschiedenen Jahreszeiten implementiert. Wenngleich die anzustrebenden optimalen 25-OH-Vitamin-D-Spiegel für die Normalbevölkerung und Athleten weiterhin wissenschaftlich umstritten sind[48, 54, 58-61], unterstützen unsere Studienergebnisse den unteren Grenzwert von 30 ng/ml 25-OH-Vitamin D zur Erhaltung der Knochengesundheit. Ob dieser Wert auch für die Erhaltung der kardiovaskulären Gesundheit und eine optimale körperliche Leistungsfähigkeit bei Leistungssportlern ausreichend ist, wird gegenwärtig intensiv untersucht.

3.2 *Einfluss eines 25-OH-Vitamin-D-Mangels auf den Blutdruck in Ruhe*

Ein Vitamin-D-Mangel wurde in vielen Beobachtungsstudien mit arterieller Hypertonie[69], einer beeinträchtigten Gefäßfunktion[70] und erhöhter Mortalität[54, 71] assoziiert. Da Vitamin-D-Rezeptoren an glatten Muskelzellen[72], Myozyten und Endothelzellen[73] zu finden sind und zudem eine Vitamin-D-regulierte Reduktion der Aktivität des Renin-Angiotensin-Aldosteron-Systems festgestellt werden konnte[74], wurde ein Kausalzusammenhang zwischen Vitamin D, Blutdruckregulation und kardiovaskulärer Gesundheit angenommen[46, 51, 71]. Diese Theorie wurde durch eine kürzlich publizierte Mendelsche Randomisierungsstudie unterstützt[52].
Allerdings haben bisherige Studien widersprüchliche Ergebnisse für die blutdrucksenkenden Wirkungen einer Vitamin-D-Supplementierung erbracht[75-77]. Diese diskrepanten Ergebnisse überraschen jedoch nicht, da meist keine Kontrolle bezüglich des Fitnessstatus – als dominierenden Prädiktor für die kardiovaskuläre Gesundheit[43, 44] – vorgenommen wurde. Wir haben den Zusammenhang zwischen Fitness, Vitamin D und kardiovaskulärer Funktion daher in einer Kohorte homogen fitter und aktiver Profisportler untersucht.

Publikation Nr. 2:
Bauer P, Kraushaar L, Hölscher S, Tajmiri-Gondai S, Dörr O, Nef H, Hamm C, Most A. Elite athletes as research model: vitamin D insufficiency associates with elevated central blood pressure in professional handball athletes. Eur J Appl Physiol. 2019 Oct;119(10):2265-2274. doi: 10.1007/s00421-019-04210-w. Epub 2019 Aug 19. PMID: 31428859.

In einer Pilotstudie untersuchten wir die Auswirkungen eines 25-OH-Vitamin-D-Mangels auf die vaskuläre Funktion und die Höhe des peripheren und zentralen Blutdruckes bei Leistungssportlern. Hierfür konnten wir 50 männliche professionelle Handballspieler im mittleren Alter von 26 (± 5) Jahren untersuchen und anhand ihres 25-OH-Vitamin-D-Spiegels in eine Gruppe mit insuffizientem (< 30 ng/ml) und eine Gruppe mit suffizientem (≥ 30 ng/ml) Spiegel einteilen. Diese Gruppen wurden bezüglich des brachialen und zentralen Blutdruckes sowie der vaskulären Funktion verglichen und wir nahmen an, dass die Athleten mit insuffizientem 25-OH-Vitamin-D-Status einen höheren Blutdruck infolge einer schlechteren vaskulären Funktion haben würden. Mit Hilfe eines validierten oszillometrischen Verfahrens wurden auf Basis der Pulswellenanalyse die physikalischen vaskulären

Funktionsparameter und der zentrale Blutdruck in Ruhe und standardisiert nach einer Wettkampfpause von sechs Wochen gemessen.

Zwischen den Athleten mit insuffizienten und denen mit suffizienten Vitamin-D-Spiegeln konnten keine Unterschiede in Alter, Gewicht, Body-Mass-Index, Herzfrequenz in Ruhe und bei maximaler Belastung sowie der Trainingshistorie gefunden werden. Die 25-OH-Vitamin-D-Werte lagen bei 41,3 ± 9 ng/ml in der suffizienten Gruppe und bei 21,1 ± 8 ng/ml in der insuffizienten Gruppe und somit jeweils deutlich oberhalb beziehungsweise unterhalb der Schwelle von 30 ng/ml. Der Anteil der Athleten mit einem insuffizienten 25-OH-Vitamin-D-Spiegel lag bei 18 % (n = 9), wohingegen 82 % (n = 41) suffiziente Werte aufwiesen. Aufgrund unserer vorhergehenden Untersuchung war dies eine überraschend niedrige Prävalenz. Wir führen dies auf eine Änderung der Verhaltensweise der Athleten mit einem gesteigerten Bewusstsein für die Erhaltung eines suffizienten Vitamin-D-Spiegels zurück, da keine Supplementation mit Vitamin D durchgeführt wurde.

Athleten mit ausreichenden 25-OH-Vitamin-D-Spiegeln zeigten sowohl einen signifikant niedrigeren zentralen diastolischen (58 ± 9 vs. 68 ± 8 mmHg, $p = 0{,}002$) als auch einen niedrigeren zentralen systolischen Blutdruck (97 ± 7 vs. 106 ± 5 mmHg, $p < 0{,}001$) im Vergleich zu den Athleten mit insuffizienten 25-OH-Vitamin-D-Spiegeln. Ferner war der mittlere zentrale Blutdruck der Gruppe mit ausreichenden 25-OH-Vitamin-D-Spiegeln signifikant niedriger als in der Gruppe mit insuffizienten 25-OH-Vitamin-D-Spiegeln (73 ± 8 gegenüber 83 ± 6,5 mmHg, $p = 0{,}001$) *(Abbildung 3)*. Auch die brachialen Blutdruckwerte waren signifikant unterschiedlich mit höheren Werten in der Gruppe mit insuffizienten Vitamin-D-Spiegeln. Allerdings konnten wir in der Gesamtkohorte keine erhöhten brachialen Blutdruckwerte oberhalb der definierten Schwellen (140 mmHg systolisch und/oder 90 mmHg diastolisch) detektieren.

Die gemessenen Werte der vaskulären Funktion bei unseren professionellen Athleten deuteten allesamt auf eine bessere vaskuläre Funktion der Athleten im Vergleich zur Normalbevölkerung hin. Die Leistungssportler unserer Studie zeigten zudem eine höhere Pulsdruckamplifikation (26 ± 5 mmHg vs. 15 ± 7 mmHg, $p < 0{,}001$) im Vergleich zur Referenzpopulation gleichen Alters[25].

Bei der Betrachtung der zentralen Blutdruckwerte fielen mehrere interessante Aspekte auf. Während der zentrale systolische Blutdruck bei den Athleten mit suffizienten Vitamin-D-Werten signifikant unterhalb der publizierten Normwerte[25] (97 ± 7 mmHg vs. 103 ± 9 mmHg, $p < 0.001$) lag, war dies bei Athleten mit insuffizienten Vitamin-D-Werten (106 ± 5 mmHg vs. 103 ± 9 mmHg, $p = 0{,}12$) nicht der Fall. Trotz des höheren brachialen und zentralen

Blutdruckes bei Athleten mit Vitamin-D-Mangel bestanden keine Unterschiede im zentralen und peripheren Pulsdruck, der Pulswellengeschwindigkeit, dem Augmentationsindex sowie in der Pulsdruckamplifikation.

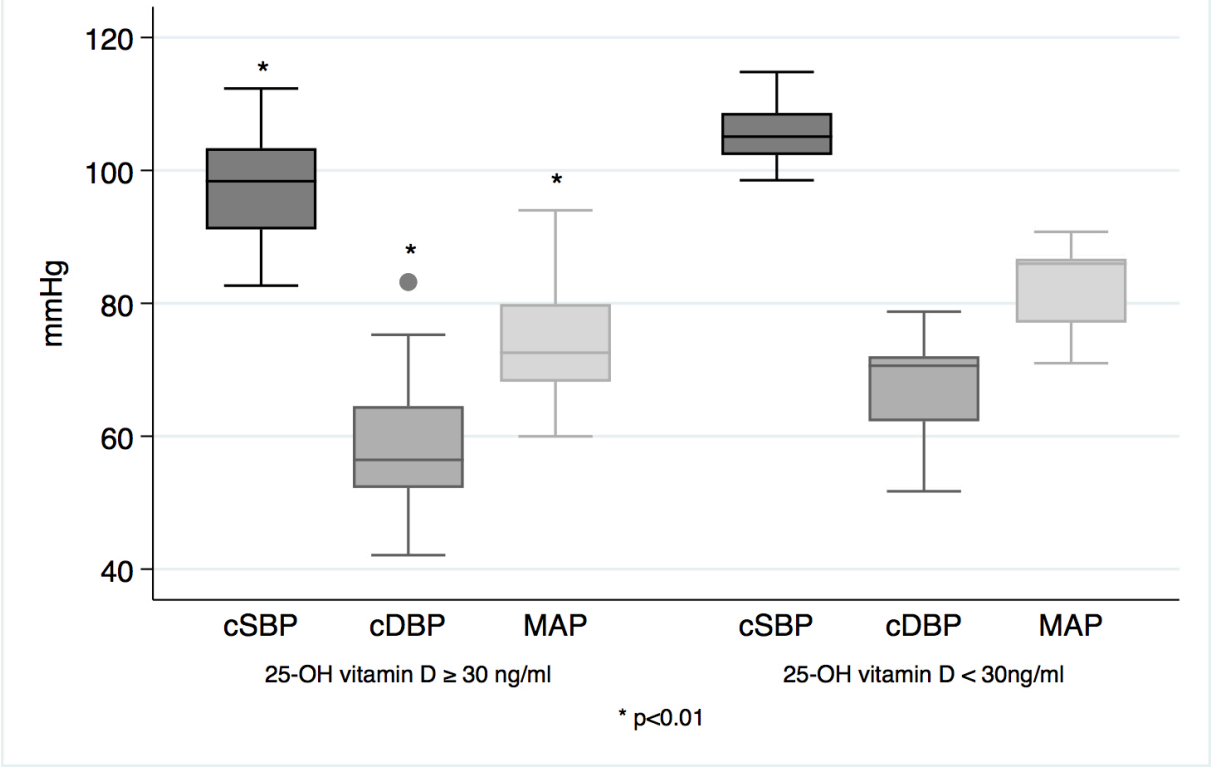

Abb. 3: Zentraler systolischer (cSBP) und diastolischer (cDBP) sowie mittlerer zentraler (MAP) Blutdruck bei Athleten mit suffizienten und insuffizienten 25-OH-Vitamin-D-Spiegeln. Dargestellt sind jeweils Boxplots mit 25/75-%-Interquartilen sowie die jeweiligen 5/95-%-Perzentile.

Zusammenfassend weisen diese Erkenntnisse darauf hin, dass Vitamin D und körperliche Fitness die kardiovaskuläre Funktion unterschiedlich beeinflussen. Daher erscheint die Untersuchung von Kohorten mit homogener Fitness geeignet, um die Auswirkungen eines Vitamin-D-Mangels auf die vaskuläre Funktion zu untersuchen. Ferner scheint eine durch körperliche Aktivität verbesserte vaskuläre Funktion bei Leistungssportlern die Auswirkungen eines Vitamin-D-Mangels in Ruhe so weit zu kompensieren, dass hieraus keine messbaren Änderungen der vaskulären Funktionsparameter resultieren.

3.3 Einfluss eines 25-OH-Vitamin-D-Mangels auf den Blutdruck unter Belastung

Aufbauend auf den Erkenntnissen der vorhergehenden Studie, in der wir eine Assoziation eines Mangels an 25-OH-Vitamin D mit höheren zentralen und brachialen Blutdruckwerten feststellen konnten, war das Ziel der nächsten Studie, die Auswirkungen eines Vitamin-D-Mangels auf die Blutdruckregulation unter Belastung zu charakterisieren. Angesichts der physiologischen Einflüsse von Vitamin D auf Endothel- und glatte Muskelzellen[72, 73] war unsere Hypothese, dass sich die in Ruhe bei Leistungssportlern noch kompensierte Einschränkung der vaskulären Funktion als Folge eines 25-OH-Vitamin-D-Mangels unter einer maximalen Belastung in Form einer gesteigerten Blutdruckantwort demaskiert. Das in unseren Studie zur Messung der zentralen Hämodynamik und Gefäßsteifigkeit genutzte validierte oszillometrische Verfahren ist aufgrund der Messmethodik[26] jedoch nicht geeignet, valide Messergebnisse der zentralen Hämodynamik unter Belastungsbedingungen zu liefern. Daher fokussierten wir uns bei dieser Untersuchung auf die Erhebung der brachialen Blutdruckwerte.

Publikation Nr. 3:

Bauer P, Kraushaar L, Dörr O, Bauer T, Nef H, Hamm CW, Most A. Association of 25-hydroxy vitamin D level with the blood pressure response to a maximum exercise test among professional indoor athletes. Eur J Appl Physiol. 2020 Aug;120(8):1931-1941. doi: 10.1007/s00421-020-04421-6. Epub 2020 Jun 25. PMID: 32588193; PMCID: PMC7340632.

Die Teilnehmer dieser Studie waren 120 männliche, kaukasische und verletzungsfreie professionelle Handball- und Eishockeysportler (Alter 25,8 ± 5,2 Jahre) unterschiedlicher Nationalität. Keiner von ihnen war ein regelmäßiger Sonnenbanknutzer, darüber hinaus wurden keine Vitamin-D-Präparate oder andere Multivitaminpräparate eingenommen. Anhand des 25-OH-Vitamin-D-Spiegels wurden analog zu unseren vorhergehenden Studien zwei Gruppen definiert und miteinander verglichen: eine Gruppe mit insuffizientem (< 30 ng/ml) und eine Gruppe mit suffizientem (≥ 30 ng/ml) Vitamin-D-Spiegel. Die 25-OH-Vitamin-D-Werte lagen bei 42,3 ± 9 ng/ml in der suffizienten Gruppe und bei 22,95 ± 5 ng/ml in der insuffizienten Gruppe und somit jeweils deutlich oberhalb beziehungsweise unterhalb

der definierten Schwelle von 30 ng/ml. Ein Vitamin-D-Mangel wurde bei 35 Athleten (29 %) festgestellt, 85 Athleten (71 %) wiesen hingegen suffiziente Werte auf.

Hinsichtlich der Baseline-Daten unterschieden sich die Athleten in beiden Gruppen nicht voneinander. Alle Athleten durchliefen einen Ausbelastungstest auf dem Fahrradergometer, bei dem stufenweise in Abständen von 2 Minuten die Belastung um 50 Watt gesteigert wurde. Währenddessen wurde jede Minute automatisiert der Blutdruck gemessen und die Herzfrequenz durchgehend mittels 12-Kanal-EKG aufgezeichnet.

Die Blutdruckantwort auf die Belastung wurde jeweils als Zunahme der systolischen und der diastolischen Blutdruckwerte von Belastungsbeginn bis zur Ausbelastung definiert. Zudem wurde eine Indexierung der Blutdruckantwort auf die jeweilige Leistung vorgenommen, indem der maximal erreichte systolische Blutdruck durch die individuelle maximale Leistung (maximal erreichte Wattzahl/Kilogramm Körpergewicht) geteilt wurde.

Alle untersuchten Athleten waren normotensiv und es gab keine Unterschiede hinsichtlich des Blutdruckes in Ruhe, des Pulsdruckes und des mittleren Blutdruckes zwischen Athleten mit insuffizienten und suffizienten 25-OH-Vitamin-D-Spiegeln.

Bei maximaler Belastung waren jedoch der systolische Blutdruck (198 ± 18 gegenüber 189 ± 19, $p = 0{,}026$) und der Pulsdruck (118 ± 18 gegenüber 109 ± 21 mmHg, $p = 0{,}021$) in der suffizienten Gruppe höher. Die individuelle Blutdruckantwort (BPR) unterschied sich jedoch nicht zwischen den beiden Gruppen ($76 \pm 20/5 \pm 6$ gegenüber $69 \pm 22/3 \pm 6$ mmHg, $p = 0{,}103$). Zudem wiesen Athleten mit suffizienten 25-OH-Vitamin-D-Werten eine höhere maximale Leistung ($3{,}99 \pm 0{,}82$ gegenüber $3{,}58 \pm 0{,}78$ W/kg, $p = 0{,}015$) auf und erreichten eine höhere Wattzahl (367 ± 78 gegenüber 333 ± 80 W, $p = 0{,}039$). Ferner fanden sich nach Indexierung der Blutdruckantwort auf die jeweilige maximale Leistung keine Unterschiede zwischen Athleten mit suffizienten und insuffizienten Vitamin-D-Spiegeln (51 ± 10 vs. 56 ± 14 mmHg×kg/W, $p = 0{,}079$) *(Tabelle 1)*.

Die 25-OH-Vitamin-D-Spiegel der Athleten korrelierten positiv mit der maximal erreichten Wattzahl ($r^2 = 0{,}373$, $p < 0{,}001$) sowie der maximalen Leistung ($r^2 = 0{,}327$, $p < 0{,}001$), während eine negative Korrelation mit der auf die Leistung indexierten Blutdruckantwort ($r^2 = -0{,}222$, $p = 0{,}015$) bestand. Die linearen Regressionsanalysen ergaben zudem, dass ein 25-OH-Vitamin-D-Spiegel ein statistisch signifikanter Prädiktor für eine höhere maximale Leistung ($r^2 = 0{,}123$, $p < 0{,}001$) und eine höhere maximale Wattzahl ($r^2 = 0{,}126$, $p < 0{,}001$) ist. Allerdings konnte der 25-OH-Vitamin-D-Spiegel die auf die Leistung indexierte Blutdruckantwort nicht vorhersagen ($r^2 = 0{,}07$, $p = 0{,}12$).

	25-OH-Vitamin D		
	≥30 ng/ml	**<30 ng/ml**	**p**
Anzahl	85 (71 %)	35 (29 %)	
25-OH-Vitamin D (ng/ml)	42,3 ± 8,9	22,95 ± 5,1	*< 0,001*
Herzfrequenz in Ruhe (/min)	58,4 ± 10,5	59,1 ± 9,4	0,748
Systolischer Blutdruck (mmHg)	122,1 ± 10	120 ± 11,6	0,333
Diastolischer Blutdruck (mmHg)	75,1 ± 7,4	76,8 ± 8,6	0,362
Pulsdruck in Ruhe (mmHg)	47 ± 11	43,5 ± 13,3	0,152
Maximale Herzfrequenz (/min)	184 ± 8,4	183,7 ± 7,2	0,862
Maximaler systolischer Blutdruck (mmHg)	197,8 ± 17,5	189,3 ± 19,4	*0,026*
Maximaler diastolischer Blutdruck (mmHg)	79,7 ± 7,4	80,4 ± 7,3	0,651
Maximaler Pulsdruck (mmHg)	118 ± 18	108,9 ± 20,8	*0,021*
Δ systolischer Blutdruck (mmHg)	75,7 ± 20	69,3 ± 21,6	0,103
Δ diastolischer Blutdruck (mmHg)	4,6 ± 5,7	3,4 ± 6,3	0,621
Maximale Watt (W)	367,2 ± 78,4	332,8 ± 79,9	*0,039*
Leistung (W/kg)	3,99 ± 0,82	3,58 ± 0,78	*0,015*
Maximaler systolischer Blutdruck/Leistung (mmHg* kg/W)	51,3 ± 10,2	55,5 ± 14,1	0,079

Tabelle 1: Vergleich der Ergebnisse des Ausbelastungstestes bei männlichen Leistungssportlern entsprechend dem 25-OH-Vitamin-D-Spiegel.

Unsere Ergebnisse waren überraschend, da wir die Hypothese aufgestellt hatten, dass Athleten mit einem Vitamin-D-Mangel höhere maximale Blutdruckwerte und eine überschießende Blutdruckreaktion im Ausbelastungstest im Vergleich zu Athleten mit

suffizienten Vitamin-D-Spiegeln aufweisen würden. Entgegen unserer Hypothese zeigte die aktuelle Studie aber, dass die Vitamin-D-Spiegel nicht mit der individuellen Blutdruckantwort oder dem maximalen systolischen Blutdruck assoziiert waren. Dies deckt sich mit den Ergebnissen von Zaleski[78], der in einer Normalbevölkerung die Assoziation zwischen Vitamin D, Blutdruckantwort bei einem Belastungstest und maximalem systolischen Blutdruck untersucht hatte. Daher scheinen die Folgen eines Vitamin-D-Mangels auf die Blutdruckregulation unter Belastung durch vaskuläre Funktionsanpassungen teilweise kompensiert werden zu können. Ferner lagen die maximalen systolischen Blutdruckwerte unserer untersuchten Athleten unterhalb der Werte, die in einer vergleichbaren Studie mit Leistungssportlern beobachtet wurden[79].

Zusammenfassend war eine wesentliche Erkenntnis dieser Studie, dass bei männlichen Leistungssportlern ein Vitamin-D-Mangel kein Risikofaktor für eine überschießende Blutdruckreaktion im Ausbelastungstest war. Die ermittelten höheren maximalen systolischen Blutdruckwerte in der Gruppe mit suffizienten Vitamin-D-Spiegeln waren Ausdruck der höheren Leistungsfähigkeit dieser Gruppe. Dies unterstreicht den Einfluss von Vitamin D auf die Leistungsfähigkeit bei Athleten, der sowohl auf die muskuloskelettalen als auch auf die kardiovaskulären Wirkungen des Hormons zurückgeführt werden kann. Zudem weist unsere Studie auf die Wichtigkeit der Indexierung der gemessenen maximalen systolischen Blutdruckwerte auf die jeweilige Leistung hin.
Weiterhin bestätigt sich unsere Annahme, dass gut trainierte Sportpopulationen eine einzigartige Gelegenheit bieten, um die modifizierenden Auswirkungen der kardiorespiratorischen Fitness auf die Assoziation von 25-OH-Vitamin D mit kardiovaskulären Risikomarkern zu untersuchen.

4. Vaskuläre Funktion, Blutdruckregulation unter Belastung und deren Einfluss auf die Leistungsfähigkeit

Aus unseren vorhergehenden Studien ergaben sich Hinweise darauf, dass die vaskuläre Funktion die individuelle Leistungsfähigkeit der Athleten sowie deren Blutdruckregulation beeinflusst. Ferner zeigte sich insbesondere in unserer Studie zum Einfluss von 25-OH-Vitamin D auf die Blutdruckregulation unter Belastung, dass eine Indexierung der Blutdruckantwort auf die jeweilige Belastung und gerade nicht die alleinige Betrachtung der maximalen systolischen Blutdruckwerte zur Beurteilung des Blutdruckverhaltens notwendig ist. Die widersprüchlichen Studienergebnisse, die im Hinblick auf den Einfluss des maximalen systolischen Blutdruckes auf das kardiovaskuläre Risiko festgehalten wurden[8, 10], unterstreichen ebenfalls die Notwendigkeit einer Änderung der bisherigen Herangehensweise.
Die Idee der Arbeitslast-indexierten Betrachtung der individuellen Blutdruckantwort bei einem klinischen Ausbelastungstest wurde für die Normalbevölkerung aufgegriffen und die Ergebnisse einer Studie von Hedman und Kollegen wurden im Jahr 2019 publiziert[9]. Hier konnte erstmalig gezeigt werden, dass der hier untersuchte SBP/MET-slope den maximal erreichten systolischen Blutdruckwerten in der Vorhersage der Sterblichkeit über 20 Jahre überlegen und ein höherer SBP/MET-slope mit einem höheren Sterblichkeitsrisiko verbunden war[9]. Zudem wies selbst die Gruppe der Männer mit niedrigem kardiovaskulären Risiko und hoher Fitness bei einem SBP/MET-slope $> 6{,}2$ mmHg/MET ein 27 % höheres Mortalitätsrisiko über 20 Jahre auf[9].
Anknüpfend an diese Erkenntnisse führte die gleiche Autorengruppe[15] zwei weitere neue Parameter ein, um die individuelle Blutdruckantwort bei einem Belastungstest zu charakterisieren: zum Ersten war dies der SBP/W-slope, der die Steigerung des systolischen Blutdruckes in Bezug zur Steigerung der Wattzahl widerspiegelt, und zum Zweiten die peak SBP/W-ratio, die den maximal erreichten systolischen Blutdruck zur maximal erreichten Wattzahl in Beziehung setzt. In einer Populationsstudie wurden für diese Parameter geschlechts- und altersspezifische Referenzwerte für die Fahrradergometrie etabliert[15].

4.1 Vaskuläre Funktion und Leistungsfähigkeit

Die erwähnten vielversprechenden neuen Parameter zur klinischen Beurteilung der Blutdruckantwort bei einem Belastungstest wurden bisher bei Athleten noch nicht untersucht. Daher wollten wir überprüfen, ob diese Parameter auch zur klinischen Beurteilung der individuellen Blutdruckantwort bei Leistungssportlern genutzt werden können oder ob Athleten spezifische Referenzwerte benötigen. Zudem war unser Ziel, zu untersuchen, ob und wie die zentrale Hämodynamik und die vaskuläre Funktion diese Parameter beeinflussen beziehungsweise inwieweit eine Prädiktion dieser Parameter durch eine vaskuläre Funktionsanalyse möglich ist.

Publikation Nr. 4:

Bauer P, Kraushaar L, Most A, Hölscher S, Tajmiri-Gondai S, Dörr O, Troidl C, Bauer T, Nef H, Hamm CW, Keller T. Impact of Vascular Function on Maximum Power Output in Elite Handball Athletes. Res Q Exerc Sport. 2019 Dec;90(4):600-608. doi: 10.1080/02701367.2019.1639602. Epub 2019 Aug 9. PMID: 31397640.

In dieser Pilotstudie untersuchten wir den Einfluss von Leistungssport auf die vaskuläre Funktion. Wir gingen von der Hypothese aus, dass Athleten in Ruhe eine bessere vaskuläre Funktion als die Kontrollgruppe aufweisen und diese mit der maximalen Leistung bei einem Ausbelastungstest korreliert. Zu diesem Zweck konnten wir 30 männliche Leistungssportler (27 ± 4 Jahre) und 10 männliche Probanden gleichen Alters (26 ± 4 Jahre) als Kontrollgruppe in die Studie einschließen.

Wir führten in beiden Gruppen einen Ausbelastungstest auf dem Fahrradergometer bei gleichzeitiger Blutdruck- und EKG-Aufzeichnung durch. Das Belastungstestprotokoll der Athleten begann mit einer Belastung von 100 W nach einer 2-minütigen Aufwärmphase, die mit 50 W durchgeführt wurde. Die Kontrollprobanden begannen mit 50 Watt nach einer Aufwärmphase mit 25 Watt. Die Belastung wurde bei den Athleten um 50 W und bei der Kontrollgruppe alle 2 Minuten um 25 Watt erhöht, bis die Erschöpfung erreicht war. Diese wurde definiert als die Unfähigkeit der Teilnehmer, die Belastung 2 Minuten lang aufrechtzuerhalten.

Zudem wurden die zentralen hämodynamischen Parameter und die vaskulären Funktionsparameter mit Hilfe eines validierten oszillometrischen Verfahrens auf Basis der Pulswellenanalyse gemessen.

Alle Teilnehmer der Studie waren normotensiv, wobei die Athleten signifikant niedrigere brachiale und zentrale Blutdruckwerte aufwiesen als die Kontrollgruppe *(Tabelle 2)*.

Zwischen Athleten und Kontrollprobanden waren jedoch keine Unterschiede in der PWV ($6{,}2 \pm 0{,}8$ gegenüber $6{,}3 \pm 0{,}5$ m/s, $p = 0{,}45$) und dem Aix@75 (-4 ± 12 % gegenüber -13 ± 15 %, $p = 0{,}06$) festzustellen. Damit konnten wir in dieser Untersuchung keine Unterschiede in den Parametern der arteriellen Gefäßsteifigkeit detektieren. Dies deckt sich mit den Beobachtungen von Tomschi et al.[36]. Allerdings ist die Datenlage zur Auswirkung von Leistungssport auf die arterielle Gefäßsteifigkeit derzeit inkonsistent[30-32], was wahrscheinlich mit den untersuchten Kollektiven und Sportarten zusammenhängt[37].

Interessanterweise konnte bei der Kontrollgruppe im Vergleich zur Athletengruppe ein niedriger Widerstandsindex (Resistance Index) bestimmt werden ($10{,}7 \pm 2$ gegenüber $15{,}9 \pm 4{,}4$, $p < 0{,}001$). Allerdings korrelierte der Widerstandsindex nur bei den Leistungssportlern mit der maximalen Leistungsfähigkeit ($r = -0{,}597$, $p < 0{,}01$). Zudem konnten durch univariate lineare Regressionsanalysen der Widerstandsindex ($R^2 = 0{,}29$, $p < 0{,}01$, *Abbildung 4*) und die VO2 max. ($R^2 = 0{,}198$, $p = 0{,}014$) als eigenständige und unabhängige Prädiktoren der maximalen Leistungsfähigkeit bei Leistungssportlern ermittelt werden, jedoch nicht in der Kontrollgruppe. Alle anderen vaskulären Funktionsparameter und Parameter der zentralen Hämodynamik korrelierten nicht mit der maximalen Leistungsfähigkeit bei Athleten und Kontrollprobanden und konnten diese demzufolge auch nicht voraussagen.

Bei Athleten wurden in Ruhe niedrigere periphere und zentrale Blutdruckwerte sowie ein höherer Widerstandsindex im Vergleich zur Kontrollgruppe gefunden, wohingegen keine Unterschiede in der PWV und dem Aix@75-Wert festzustellen waren. Jedoch wies die Kontrollgruppe eine signifikant niedrigere Leistungsfähigkeit und einen signifikant höheren maximalen systolischen Blutdruck auf. Dies kann mit einer verbesserten vaskulären Funktion bei Sportlern erklärt werden, die sich insbesondere unter Belastungsbedingungen bemerkbar macht. Die inverse Korrelation zwischen Widerstandsindex und höherer Leistungsfähigkeit bei Athleten in unserer Studie unterstreicht den Zusammenhang zwischen Gefäßfunktion, Blutdruckregulation und Leistungsfähigkeit. Dies stimmt auch mit den Untersuchungen von Green et al.[80, 81] überein, bei denen der peripher-vaskuläre Widerstand als wichtige

Komponente sowohl der Blutdruckregulation als auch der Leistungsfähigkeit identifiziert wurde.

	Athleten (n = 30)	Kontrollen (n = 10)	p
Alter (Jahre)	27 ± 4	26 ± 4	0,65
Größe (cm)	191 ± 4,7	182 ± 7,8	*< 0,001*
Gewicht (kg)	94,2 ± 10,7	82,8 ± 10,2	*0,02*
BMI (kg/m²)	25,7 ± 2,3	25 ± 2,6	0,58
Herzfrequenz in Ruhe (/min)	53 ± 7	74 ± 5	*0,01*
Systolischer Blutdruck (mmHg)	123 ± 8	129 ± 9	*0,02*
Diastolischer Blutdruck (mmHg)	61 ± 9	74 ± 9	*< 0,001*
Zentraler systolischer Blutdruck (mmHg)	102 ± 9	110 ± 8	*0,01*
Zentraler diastolischer Blutdruck (mmHg)	60 ± 9	74 ± 9	*< 0,001*
Zentraler Pulsdruck in Ruhe (mmHg)	42 ± 6,5	36 ± 4,4	*< 0,01*
Mittlerer zentraler Blutdruck (mmHg)	74 ± 8	88 ± 10	*< 0,001*
Pulswellengeschwindigkeit (m/s)	6,2 ± 0,82	6,3 ± 0,48	0,45
Augmentationsindex@75 (%)	-4 ± 12	-13 ± 15	0,06
Resistance-Index	15,88 ± 4,43	10,66 ± 2,04	*< 0,001*
Maximale Herzfrequenz (/min)	172 ± 10	188 ± 10	*< 0,001*
Maximaler systolischer Blutdruck (mmHg)	189 ± 18	203 ± 24	*0,04*
Maximale Watt (W)	343 ± 77	202 ± 43	*< 0,001*
Leistung (W/kg)	3,55 ± 0,54	2,46 ± 0,55	*< 0,001*
VO2 max. (mlO2/kg*min)	50,88 ± 6,8	37,4 ± 5,1	*< 0,001*

Tabelle 2: Vergleich der klinischen Charakteristika und der vaskulären Funktionsanalyse zwischen männlichen Athleten und männlichen Kontrollpersonen.

Regelmäßige körperliche Aktivität führt zu strukturellen und funktionellen Anpassungsmechanismen, die bisher noch nicht im Detail geklärt sind[81]. Die nichtinvasive Beurteilung der Gefäßfunktion mittels Oszillometrie unter Verwendung direkter physikalischer Parameter der Arterienfunktion ist ein neuer und vielversprechender Weg, um Einblicke in dieses Thema zu gewinnen. Diese Methode könnte dazu beitragen, die Auswirkungen des Profisports auf kardiovaskuläre Anpassungen und die Beziehung zur kardiorespiratorischen Fitness aufzudecken. Darüber hinaus scheint die Messung direkter physikalischer Parameter der Gefäßfunktion zur Quantifizierung des kardiovaskulären Risikos auch in gesunden Populationen geeignet zu sein.

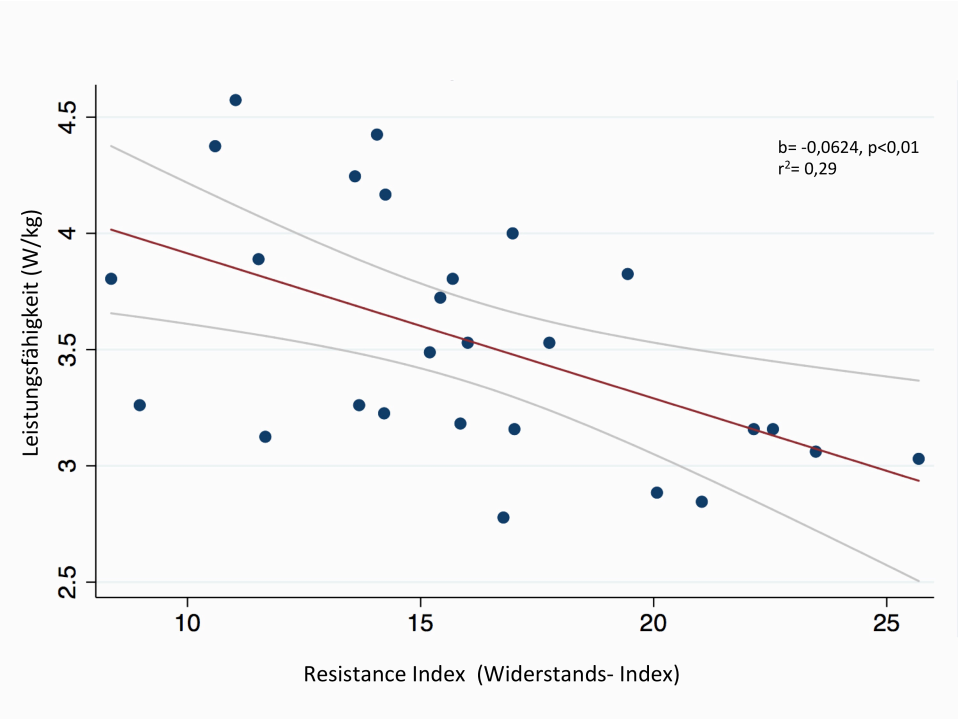

Abb.. 4: Leistungsfähigkeit in Abhängigkeit vom Widerstandsindex (Resistance-Index).
Die rote Linie stellt die Regressionsgerade dar.
Die beiden grauen Linien spiegeln das 5-%- und das 95-%-Konfidenzintervall wider.

Zusammenfassend konnten wir mit dieser Untersuchung wichtige Erkenntnisse zum Einfluss von Leistungssport auf die vaskuläre Funktion und die zentrale Hämodynamik gewinnen. Zudem unterstreicht die Studie den Zusammenhang zwischen Gefäßfunktion, Blutdruckregulation und Leistungsfähigkeit. Unsere Ergebnisse deuten darauf hin, dass die Unterschiede der vaskulären Funktion zwischen Athleten und Kontrollen insbesondere unter Belastungsbedingungen zum Vorschein kommen und zu einer unterschiedlichen Blutdruckregulation und Leistungsfähigkeit führen.

4.2 Arbeitslast-indexierte Parameter der Blutdruckregulation und Leistungsfähigkeit bei Leistungssportlern

Das Ziel der folgenden Arbeit war es, den neu eingeführten Arbeitslast-indexierten Parameter SBP/MET-slope, der in einer männlichen Kohorte mit der Sterblichkeit über einen Zeitraum von 20 Jahren assoziiert war[9], in einer Gruppe männlicher Leistungssportler zu evaluieren. Aufbauend auf unseren vorhergehenden Studienergebnissen nahmen wir zudem an, durch die Anwendung dieses Parameters nicht nur Unterschiede in der Blutdruckregulation, sondern auch in der Leistungsfähigkeit ermitteln zu können.

Publikation Nr. 5:
Bauer P, Kraushaar L, Dörr O, Nef H, Hamm CW, Most A. Workload-indexed blood pressure response to a maximum exercise test among professional indoor athletes. Eur J Prev Cardiol. 2020 May 6:2047487320922043. doi: 10.1177/2047487320922043. Epub ahead of print. PMID: 32375548.

In diese Querschnittsstudie wurden 142 gesunde männliche Leistungssportler aus dem Bereich Handball und Eishockey aufgenommen. Alle Athleten wiesen einen normalen Blutdruck auf und wurden einem standardisierten Ausbelastungstest auf dem Fahrradergometer zugeführt. Während des Testes wurden minütlich automatisierte brachiale Blutdruckmessungen vorgenommen und die Herzfrequenz kontinuierlich aufgezeichnet.
Die geleisteten MET wurden mit Hilfe der etablierten Formel für die Fahrradergometrie berechnet[13] und die Leistungsfähigkeit als geleistete Watt pro Kilogramm Körpergewicht angegeben. Ferner wurden die maximalen Herzfrequenz-, Blutdruck- und Wattwerte erhoben. Die Berechnung des SBP/MET-slopes erfolgte analog zur Publikation von Hedman et al.[9]. Basierend auf den vorgeschlagenen und untersuchten Quartilen des SBP/MET-slopes wurden die Athleten in Gruppen unterteilt und miteinander verglichen[9]. Das erste Quartil (I) wurde definiert als < 4,3 mmHg/MET, das zweite Quartil (II) als 4,3–6,2 mmHg/MET, das dritte Quartil (III) als > 6,2–9 mmHg/MET und das vierte als > 9 mmHg/MET.

Bei der Betrachtung der gesamten Studienpopulation zeigte sich ein mittlerer SBP/MET-slope von 5,4 ± 1,7 mmHg/MET, ein maximaler systolischer Blutdruck von 197 ± 20,3 mmHg und eine Leistungsfähigkeit von 3,8 ± 0,85 W/kg. Die maximalen systolischen Blutdruckwerte

liegen damit im gleichen Bereich wie in unserer vorangegangenen Studie, höher als bei männlichen Olympiateilnehmern aus Italien[11] (190 ± 20 mmHg) und niedriger als bei männlichen Profisportlern unterschiedlicher Disziplinen aus Deutschland[79] (204 ± 22 mmHg). Diese Unterschiede können auf die unterschiedliche Leistungsfähigkeit der Studienpopulationen zurückgeführt werden. So war bei Caselli et al.[11] die Leistungsfähigkeit niedriger (268 ± 53 W) als bei unserer Studie (351 ± 79 W, 3,8 ± 0,85 W/kg), wohingegen bei Pressler et al.[79] eine höhere Leistungsfähigkeit vorlag (4,15 ± 0,61 W/kg). Leider nahmen beide genannten Studien keine Indexierung auf die Belastung vor. Sie belegen jedoch wiederum die Notwendigkeit zur belastungsindexierten Betrachtungsweise der Blutdruckantwort auf einen Belastungstest, um eine klare Differenzierung des Blutdruckverhaltens unter Belastung vornehmen zu können.

Nach Aufteilung entsprechend des SBP/MET-slopes konnten wir 42 Athleten (30 %) dem ersten Quartil (I), 56 Athleten (39 %) dem zweiten Quartil (II) und 44 Athleten (31 %) dem dritten Quartil (III) zuordnen. Da der höchste berechnete SBP/MET-slope dieser Studie 8,8 mmHg/MET betrug, wurde kein Athlet dem vierten Quartil (IV) zugeordnet. Zwischen den Gruppen gab es keine signifikanten Unterschiede in den anthropometrischen Daten, den Trainingsdaten sowie den Blutdruck- und Herzfrequenzwerten in Ruhe. Auch zeigten sich keine Unterschiede in der erreichten maximalen Herzfrequenz *(Tabelle 3)*.
Allerdings konnten wir hochsignifikante Unterschiede in den maximalen systolischen Blutdruckwerten, im maximalen Pulsdruck, im systolischen Blutdruckanstieg sowie in der Leistungsfähigkeit und in der erreichten MET detektieren. So wies die Gruppe I (< 4,3 mmHg/MET) signifikant niedrigere maximale systolische Blutdruckwerte auf, besaß allerdings gleichzeitig eine signifikant höhere Leistungsfähigkeit als die anderen Gruppen *(Tabelle 3)*. Diese Ergebnisse waren auf den ersten Blick überraschend, da wir von einer linearen Beziehung zwischen systolischem Blutdruck und steigender Belastung ausgegangen waren. Demnach erwarteten wir, dass Athleten mit einem höheren maximalen systolischen Blutdruck ein besseres Leistungsniveau im Vergleich zu Athleten mit einem niedrigeren maximalen systolischen Blutdruck aufweisen würden. Entgegen dieser Erwartung ergab jedoch die aktuelle Studie, dass Athleten mit dem geringsten systolischen Blutdruckanstieg und dem niedrigsten maximalen systolischen Blutdruckwert die höchste Leistungsfähigkeit zeigten.

	SBP/MET-slope			p
	< 4,3	**4,3–6,2**	**> 6,2–9,0**	
Anzahl	42 (30 %)	56 (39 %)	44 (31 %)	ns
Alter (Jahre)	26,6 ± 4,7	26,6 ± 5,3	25,1 ± 5	ns
Größe (cm)	190,1 ± 5,8	188,6 ± 7,1	190,4 ± 7,1	ns
Gewicht (kg)	92,9 ± 9,3	91,9 ± 11	94,2 ± 10,4	ns
BMI (kg/m²)	25,6 ± 1,4	25,7 ± 2	26 ± 2,2	ns
Training pro Woche (h)	18,4 ± 3,3	17,5 ± 3,2	18,2 ± 2,7	ns
Herzfrequenz in Ruhe (/min)	55,3 ± 9	58 ± 9,8	53,6 ± 9	ns
Systolischer Blutdruck (mmHg)	125,2 ± 10,4	120,6 ± 9,4	123 ± 9,5	ns
Diastolischer Blutdruck (mmHg)	77,4 ± 7,6	76,6 ± 7,3	75,1 ± 6,7	ns
Pulsdruck in Ruhe (mmHg)	47,8 ± 11,1	44 ± 9,6	47,8 ± 10,7	ns
Maximale Herzfrequenz (/min)	176,9 ± 9,5	177,6 ± 10	179,1 ± 11,4	ns
Maximaler systolischer Blutdruck (mmHg)	180,1 ± 13,4 */**	195,1 ± 14,9 *	215,6 ± 16,1	*< 0,001*
Maximaler diastolischer Blutdruck (mmHg)	82,6 ± 7,3	86,1, ± 8,7	85,7 ± 7,9	ns
Maximaler Pulsdruck (mmHg)	97,6 ± 13,6 */**	109 ± 16,6 *	129,8 ± 16,4	*< 0,001*
Δ systolischer Blutdruck (mmHg)	55 ± 13 */**	74,5 ± 14 *	92,6 ± 12,2	*< 0,001*
Δ diastolischer Blutdruck (mmHg)	5 ± 6 *	9,5 ± 8,6	10,6 ± 10	*< 0,05*
Maximale Watt (W)	392,2 ± 47,1 */**	352,2 ± 56,6	311,9 ± 45,6	*< 0,05*
Leistung (W/kg)	4,2 ± 1 */**	3,9 ± 0,7	3,3 ± 0,5	*< 0,05*
Metabolisches Äquivalent (MET)	16,7 ± 4 */**	15,4 ± 2,6	13,4 ± 1,7	*< 0,05*
SBP/MET-slope (mmHg/MET)	3,6 ± 0,6 */**	5,2 ± 0,5 *	7,6 ± 1	*< 0,001*

Tabelle 3: Vergleich der Ergebnisse der kardiovaskulären Untersuchungen bei männlichen Leistungssportlern entsprechend der SBP/MET-slope Einteilung des Belastungstestes.
ns = nicht signifikant; *= p < 0,001 vs. > 6,2-9 mmHg/MET; **= p < 0,001 vs. 4,3-6,2 mmHg/MET

Diese Ergebnisse stimmen mit den Beobachtungen einer anderen Studie überein, welche die Auswirkungen des Blutdruckes in Ruhe auf die Leistungsfähigkeit (VO2 max.) bei Leistungssportlern untersucht hat[82]. Darin war bereits bei einem systolischen Blutdruck > 130 mmHg in Ruhe eine schlechtere Leistungsfähigkeit im Vergleich zu einem systolischen Blutdruck < 130 mmHg festgestellt worden. Zudem konnte bei diesen Athleten ein höherer maximaler systolischer Blutdruck (196 ± 18 mmHg) im Vergleich zu den Athleten mit einem systolischen Blutdruck in Ruhe < 130 mmHg (182 ± 18 mmHg) gemessen werden[82]. Interessanterweise bestanden in dieser Kohorte[82] bereits in Ruhe signifikante Unterschiede im Pulsdruck, was auf eine bereits bestehende vaskuläre Funktionseinschränkung in Ruhe hindeutet. Dies war in unserer Studienpopulation nicht der Fall; die Unterschiede der verschiedenen Gruppen wurden erst unter Belastungsbedingungen apparent. Zudem konnten wir eine sehr gute Korrelation des Δ im systolischen Blutdruck (ΔSBP) mit dem SBP/MET-slope ($r = 0{,}784$, $p < 0{,}001$) feststellen, darüber hinaus war ein höheres ΔSBP ein starker Prädiktor eines höheren SBP/MET-slopes ($r^2 = 0{,}616$, $p < 0{,}001$). Aus diesem Grund scheinen der SBP/MET-slope und das ΔSBP sensitivere Marker einer vaskulären Funktionseinschränkung zu sein als der Pulsdruck in Ruhe bei Individuen ohne strukturelle kardiovaskuläre Erkrankung.

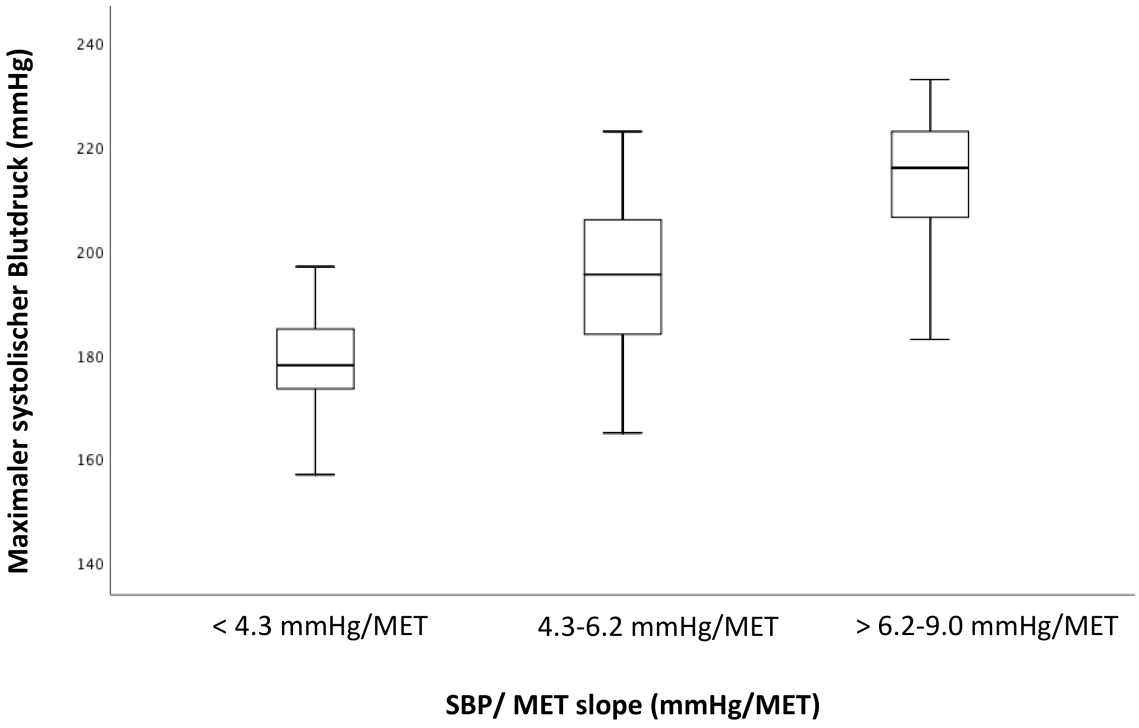

Abb. 5: Unterschiede des maximalen systolischen Blutdruckes bei männlichen Leistungssportlern entsprechend der SBP/MET-slope-Einteilung. MET: Metabolisches Äquivalent.

Zusammenfassend konnten wir mit unserer Untersuchung des SBP/MET-slopes bei männlichen Leistungssportlern zeigen, dass er auch in diesen Kohorten herangezogen werden kann, um eine Charakterisierung der Blutdruckantwort unter Belastung vorzunehmen. Zudem zeigen unsere Ergebnisse auf, dass der als normal vorgeschlagene SBP/MET-slope von 10 mmHg/MET[13] keineswegs eine normale Blutdruckantwort bei Leistungssportlern widerspiegelt, sondern allenfalls als oberes Limit angesehen werden kann.

Ferner konnten wir erstmalig bei Leistungssportlern demonstrieren, dass ein steigender SBP/MET-slope mit einem höheren maximalen systolischem Blutdruck, einem höheren maximalen Pulsdruck und einem höheren ΔSBP, allerdings mit einer niedrigeren absoluten und relativen Leistungsfähigkeit, assoziiert ist. Diese Resultate unterstreichen den Zusammenhang zwischen vaskulärer Funktion, Blutdruckregulation und Leistungsfähigkeit bei Leistungssportlern und bestätigen unsere vorhergehenden Untersuchungen. Die Methodik der Erfassung der zentralen Hämodynamik und der vaskulären Funktion mittels nichtinvasiver Methoden bietet demnach eine weiterführende Möglichkeit, akzeptierte Schwellenwerte für die neuen Parameter der Arbeitslast-indexierten Blutdruckregulation unter Belastung bei Athleten zu definieren.

4.3 Blutdruckregulation bei Athleten und Nichtathleten

Durch unsere bisherigen Untersuchungen konnten wir zeigen, dass der SBP/MET-slope bei männlichen Leistungssportlern zur klinischen Beurteilung der Blutdruckregulation angewendet werden kann und dass der früher vorgeschlagene Normwert von 10 mmHg/MET[13] deutlich zu hoch angesetzt ist.

Da die vaskuläre Funktion unmittelbare Folgen auf die Blutdruckregulation und Leistungsfähigkeit bei Athleten hat, ist eine zusätzliche Analyse der zentralen Hämodynamik und vaskulären Funktion bei der Implementierung neuer Normwerte der Arbeitslast-indexierten Blutdruckantwort hilfreich.

Kürzlich wurden neue alters- und geschlechtsspezifische Normwerte für eine Arbeitslast-indexierte Betrachtung der Blutdruckantwort bei einem Fahrradergometertest definiert[15]. Diese wurden jedoch bisher nicht bei Leistungssportlern geprüft, daher war es unklar, inwieweit sie bei dieser Kohorte angewendet werden können beziehungsweise ob bei Leistungssportlern eigene Grenzwerte definiert werden müssen. Vor diesem Hintergrund untersuchten wir in der folgenden Arbeit die neuen Arbeitslast-indexierten Parameter der Blutdruckantwort bei männlichen Leistungssportlern und männlichen Kontrollpersonen. Zusätzlich wurde evaluiert, ob und wie die zentrale Hämodynamik und die vaskuläre Funktion diese Parameter beeinflusst beziehungsweise inwieweit eine Prädiktion dieser Parameter durch eine vaskuläre Funktionsanalyse möglich ist.

Publikation Nr. 6:

Bauer P, Kraushaar L, Hoelscher S, Weber R, Akdogan E, Keranov S, Dörr O, Nef H, Hamm CW, Most A. Blood Pressure Response and Vascular Function of Professional Athletes and Controls. Sports Med Int Open. 2021 Apr 19;5(2):E45-E52. doi: 10.1055/a-1400-1897. PMID: 33889714; PMCID: PMC8055378.

Aufgrund unserer Voruntersuchungen zur Arbeitslast-indexierten Blutdruckantwort nahmen wir an, dass sich die Blutdruckregulation unter Belastung zwischen Athleten und Kontrollgruppe unterscheidet, dass allerdings kein Unterschied im maximal gemessenen systolischen Blutdruck zu sehen sein wird.

Wir untersuchten diese Hypothese an insgesamt 125 männlichen Probanden, dabei wurden 95 Leistungssportler und 30 Kontrollpersonen in die Studie eingeschlossen. Die beiden Gruppen unterschieden sich nicht in Alter und Geschlecht, jedoch waren die Athleten größer (188,5 ± 7,2 vs. 183,8 ± 6,2 cm, p = 0,002) und schwerer (91,5 ± 10,7 vs. 85,1 ± 8,3 kg, p = 0,003) als die Kontrollgruppe und wiesen eine niedrigere Ruheherzfrequenz (57,2 ± 10,3 vs. 70,1 ± 13,6/min, p < 0,001) und einen niedrigeren systolischen Blutdruck (123 ± 10,2 vs. 129 ± 11,5 mmHg, p = 0,013) auf. Bei Betrachtung der zentralen Hämodynamik und der vaskulären Funktion konnte bei Leistungssportlern ein signifikant geringerer zentraler diastolischer Blutdruck (63 ± 9,7 vs. 69 ± 9,3 mmHg, p = 0,003) und eine geringere Pulswellengeschwindigkeit (6,4 ± 0,92 vs. 7,2 ± 1,5 m/s, p = 0,001) im Vergleich zu den Kontrollprobanden gemessen werden.

Alle Studienteilnehmer führten einen Ausbelastungstest nach Stufenprotokoll auf dem Fahrradergometer durch. Hierbei wurde bei Athleten die Belastung mit 100 W begonnen und im Abstand von 2 Minuten um 50 W gesteigert; bei der Kontrollgruppe startete der Test mit 50 W und wurde alle 2 Minuten um 25 W gesteigert. Währenddessen wurde jede Minute automatisiert der Blutdruck gemessen und die Herzfrequenz durchgehend mittels 12-Kanal-EKG aufgezeichnet.

Zur Indexierung des systolischen Blutdruckanstieges in Bezug auf die Arbeitslast bei der Fahrradergometrie wurden hierbei entsprechend der Publikation von Hedman et al.[15] der SBP/W-slope, der die Steilheit der systolischen Blutdruckantwort in Bezug zur Steigerung der Wattzahl widerspiegelt, und die sogenannte peak SBP/W-ratio als Quotient aus maximal erreichtem systolischen Blutdruckwert und maximal erreichter Wattzahl errechnet. Die Berechnung des SBP/MET-slopes erfolgte, wie bereits in unserer vorhergehenden Untersuchung, analog zur Originalpublikation[9]. Wie in den vorangegangenen Studien wurden auf Basis der Pulswellenanalyse die physikalischen vaskulären Funktionsparameter und der zentrale Blutdruck mit Hilfe eines validierten oszillometrischen Verfahrens gemessen.

Erwartungsgemäß erreichten die Leistungssportler höhere Watt- (339 ± 64 vs. 211 ± 35 W, p < 0,001) und MET-Werte (13,9 ± 2,5 vs. 9,9 ± 1,4 MET, p < 0,001) und wiesen eine höhere Leistungsfähigkeit (3,73 ± 0,8 vs. 2,5 ± 0,44 W/kg, p < 0,001) als die Kontrollgruppe auf. Dennoch waren alle Arbeitslast-indexierten Parameter der Blutdruckantwort signifikant niedriger als in der Kontrollgruppe *(Tabelle 4)*.

	Athleten (n = 95)	Kontrollgruppe (n = 30)	p
Zentraler systolischer Blutdruck (mmHg)	99 ± 8	102 ± 9,3	0,052
Zentraler diastolischer Blutdruck (mmHg)	63 ± 9,7	69 ± 9,3	*0,003*
Zentraler Pulsdruck in Ruhe (mmHg)	42 ± 6,5	36 ± 4,4	*< 0,01*
Mittlerer zentraler Blutdruck (mmHg)	76 ± 10	82 ± 9,8	*0,005*
Pulswellengeschwindigkeit (m/s)	6,4 ± 0,92	7,2 ± 1,5	*0,001*
Augmentationsindex@75 (%)	-18,6 ± 10	-16 ± 10	0,38
Resistance-Index	16,4 ± 6,3	17,7 ± 7,4	0,346
Maximale Herzfrequenz (/min)	179,4 ± 9,8	187,1 ± 9,9	*< 0,001*
Maximaler systolischer Blutdruck (mmHg)	200,4 ± 20,1	197 ± 18,1	0,358
Maximale Watt (W)	339,2 ± 64	211 ± 35,2	*< 0,001*
Leistung (W/kg)	3,73 ± 0,8	2,5 ± 0,44	*< 0,001*
SBP/MET-slope (mmHg/MET)	6,2 ± 1,8	7,85 ± 1,8	*< 0,001*
SBP/Watt-slope (mmHg/W)	0,34 ± 0,13	0,44 ± 0,12	*< 0,001*
Peak SBP/Watt-ratio (mmHg/W)	0,61 ± 0,12	0,95 ± 0,17	*< 0,001*

Tabelle 4: Vergleich der vaskulären Funktionsanalyse, der Ergebnisse des Ausbelastungstestes und der neuen Arbeitslast-indexierten Marker der Blutdruckantwort zwischen Athleten und Kontrollgruppe.

Bei Betrachtung der Arbeitslast-indexierten Parameter der Blutdruckantwort der Leistungssportler fällt auf, dass die Werte für den SBP/MET-slope (6,2 ± 1,8 vs. 6,4 mmHg/MET) und den SBP/W-slope (0,34 ± 0,13 vs. 0,33 ± 0,11 mmHg/W) vergleichbar mit den publizierten Normwerten waren, wohingegen die peak SBP/W-ratio (0,61 ± 0,12 vs. 0,73 ± 0,11 mmHg/W) deutlich niedriger lag. Dies deutet darauf hin, dass die peak SBP/W-ratio relevant durch den Fitnesszustand beeinflusst wird. Daher scheinen Leistungssportler aufgrund der höheren erreichten maximalen Wattwerte niedrigere Normwerte für diesen Parameter zu benötigen. Somit ist die peak SBP/W-ratio in athletischen Populationen nicht in

gleicher Weise zu verwenden wie in Normalpopulationen. Hingegen scheinen der SBP/MET-slope und der SBP/W-slope weniger durch die körperliche Fitness beeinflusst zu sein. In der Betrachtung der Blutdruckantwort während des Belastungstestes sticht ins Auge, dass die Kurve der Blutdruckantwort bei Athleten gegenüber den Kontrollprobanden nach rechts verschoben zu sein scheint *(Abbildung 6)*.

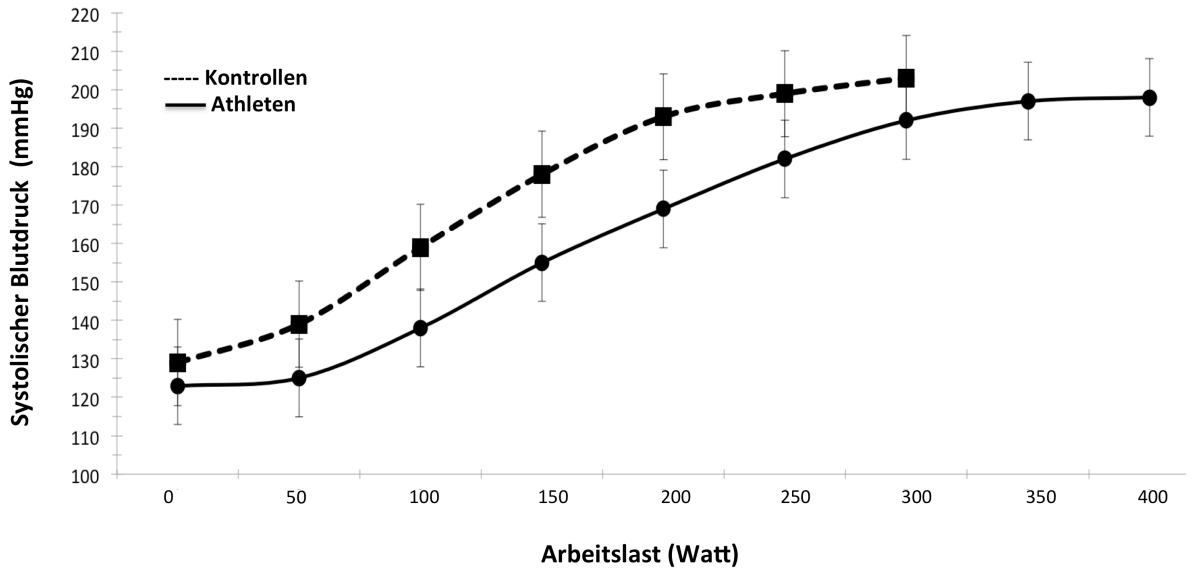

Abb. 6: Unterschiedliches systolisches Blutdruckverhalten bei einem Ausbelastungstest zwischen Athleten und Kontrollgruppe. Dargestellt sind die Mittelwerte mit Standardabweichung.

Die ermittelten systolischen Blutdruckwerte lagen in jeder verglichenen Belastungsstufe bei Athleten niedriger als bei den Kontrollpersonen. Interessanterweise zeigt sich insbesondere zu Beginn der Belastung ein signifikanter Unterschied der diastolischen Blutdruckwerte zwischen den Gruppen, wofür wohl die größere Vasodilatation der Muskelgefäße bei Leistungssportlern ursächlich ist. Trotz der Unterschiede der vaskulären Funktion zwischen Leistungssportlern und Kontrollgruppe korrelierte keiner der in Ruhe erhobenen vaskulären Funktionsparameter mit den Arbeitslast-indexierten Parametern der Blutdruckantwort. Demzufolge war es auch nicht möglich, die individuelle Blutdruckantwort anhand der in Ruhe gemessenen Werte vorauszusagen. Dies steht im Widerspruch zu einer kürzlich publizierten Studie, die eine überschießende Blutdruckantwort bei jungen Menschen mit einer erhöhten PWV assoziierte[38]. Allerdings wurden in dieser keine Athleten untersucht, die Ergebnisse wurden nicht nach Geschlechtern aufgeteilt und die Definition der überschießenden Blutdruckantwort wurde nur anhand der absoluten maximalen systolischen Blutdruckwerte vorgenommen[38]. Somit ist zwar keine direkte Vergleichbarkeit gegeben,

jedoch weisen beide Studien auf den Einfluss der vaskulären Funktion auf die Blutdruckregulation unter Belastung hin. Leider konnten wir in unserer Studie aufgrund der oszillometrischen Messmethodik keine Messung der vaskulären Parameter unter Belastung vornehmen.

Zusammenfassend wird das Konzept der Arbeitslast-indexierten Betrachtung der Blutdruckantwort durch die Ergebnisse dieser Studie ohne Einschränkung unterstützt. Obwohl sich die maximalen systolischen Blutdruckwerte zwischen Athleten und Kontrollgruppe nicht wesentlich unterscheiden (200 ± 20 vs. 197 ± 18 mmHg, $p = 0{,}358$), zeigen sich in den verschiedenen Belastungsstufen unterschiedliche Blutdruckwerte. Bei prozentualer Indexierung der Blutdruckwerte auf die individuell erreichte maximale Wattzahl kommen bei Athleten und Kontrollen nahezu deckungsgleiche Kurven zum Vorschein *(Abbildung 7)*. Somit konnten wir durch unsere Studie die Anwendbarkeit des SBP/MET-slopes und des SBP/W-slopes für männliche Leistungssportler analog zu den publizierten Referenzwerten der männlichen und altersgleichen Normalbevölkerung bestätigen. Hiedurch wird die Beurteilung der Blutdruckantwort bei einem Ausbelastungstest von Athleten, beispielsweise im Rahmen der Sporttauglichkeitsuntersuchung, vereinfacht. Zudem konnten wir zeigen, dass für die peak SBP/W-ratio bei Athleten infolge der besseren Leistungsfähigkeit niedrigere Referenzwerte im Vergleich zur Normalbevölkerung angesetzt werden müssen.

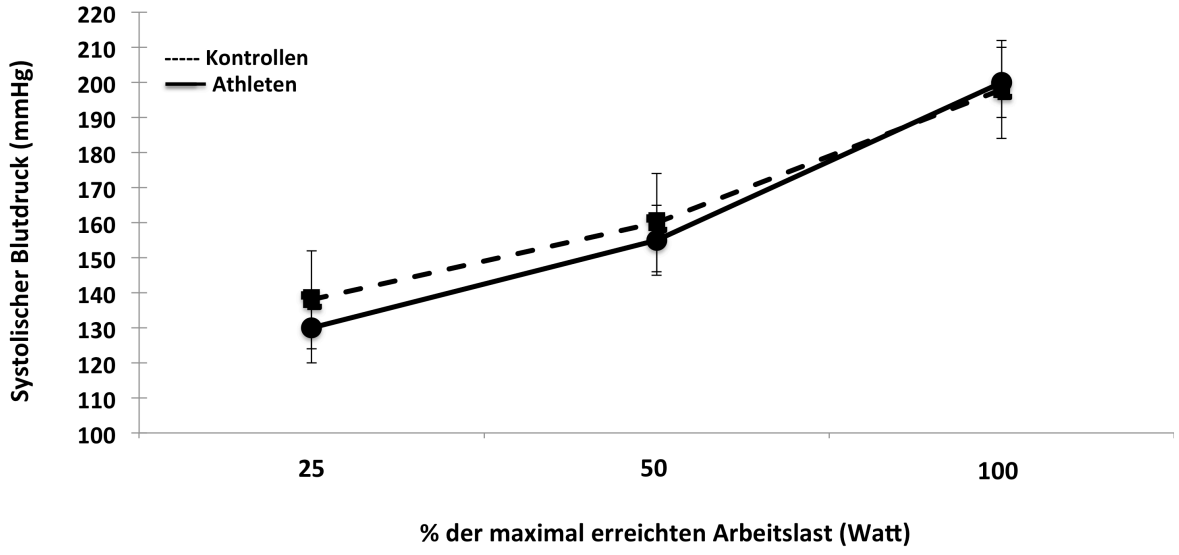

Abb. 7: Systolisches Blutdruckverhalten von Athleten und Kontrollgruppe, indexiert auf die individuell erreichte maximale Arbeitslast. Dargestellt sind die Mittelwerte mit Standardabweichung.

4.4 Geschlechtsspezifische Unterschiede der Blutdruckregulation bei Leistungssportlern

Zahlreiche Studienergebnisse weisen auf eine unterschiedliche Blutdruckregulation in Ruhe zwischen Frauen und Männern hin[83-85]. Die sympathische Nervenaktivität, das Renin-Angiotensin-System, die β-adrenerge Vasodilatation, der periphere Gefäßwiderstand, die arterielle Gefäßsteifigkeit sowie der Einfluss von Sexualhormonen wurden als wesentliche physiologische Einflussfaktoren dieser geschlechtsspezifischen Unterschiede identifiziert[83-89]. Es ist außerdem anzunehmen, dass auch die Blutdruckregulation unter Belastungsbedingungen geschlechtsspezifische Unterschiede aufweist. In den europäischen Leitlinien aus dem Jahr 2013[14] fanden sich entsprechend unterschiedliche Referenzwerte für die maximalen systolischen Blutdruckwerte bei einem Belastungstest für Männer (< 210 mmHg) und Frauen (< 190 mmHg). Allerdings wurde diese Unterscheidung in den darauffolgenden aktuell gültigen Leitlinien aufgegeben und stattdessen postuliert, dass es keinen Konsens über eine normale Blutdruckantwort bei einem Belastungstest gebe[2].
Kürzlich wurden jedoch neue alters- und geschlechtsspezifische Referenzwerte für die Arbeitslast- indexierte Blutdruckantwort bei einem Fahrradergometertest publiziert[15].
Bemerkenswerterweise waren diese angegebenen Normwerte bei Frauen deutlich höher als bei Männern, was auf einen steileren Anstieg des Blutdruckes während der Belastung hinweist[15]. Es wird angenommen, dass diese geschlechtsspezifischen Unterschiede wesentlich durch die Gefäßfunktion moduliert werden[15, 38, 84, 90, 91] und daher möglicherweise durch Messung der zentralen Hämodynamik und der vaskulären Funktion aufgedeckt werden können[15].
Da diese Arbeitslast-indexierten Parameter der Blutdruckantwort bei weiblichen Leistungssportlern noch nicht untersucht wurden und es nicht bekannt war, ob eine Übertragung der Ergebnisse aus der Normalpopulation für Leistungssportler möglich ist, untersuchten wir in der folgenden Arbeit die neuen Arbeitslast-indexierten Parameter der Blutdruckantwort bei männlichen und weiblichen Leistungssportlern gleichen Alters. Zudem wurde evaluiert, ob es geschlechtsspezifische Unterschiede der zentralen Hämodynamik und der vaskulären Funktion gibt, welche diese Parameter beeinflussen.

Publikation Nr. 7:

Bauer P, Kraushaar L, Dörr O, Nef H, Hamm CW, Most A. Sex differences in workload-indexed blood pressure response and vascular function among professional athletes and their utility for clinical exercise testing. Eur J Appl Physiol. 2021 Jul;121(7):1859-1869. doi: 10.1007/s00421-021-04656-x. Epub 2021 Mar 12. PMID: 33709207; PMCID: PMC8192366.

Die Teilnehmer dieser Studie waren 72 gesunde Leistungssportler, bestehend aus 47 Handballspielern und 25 Fußballspielerinnen gleichen Alters (21,6 ± 1,7 vs. 21,1 ± 2 Jahre, p = 0,365). Die Sportlerinnen wurden während der frühen Follikelphase oder in der Placebo-Phase der hormonellen Kontrazeption untersucht. Vier Athletinnen nahmen orale Kontrazeptiva der vierten Generation ein. Alle Probanden wurden einer körperlichen Untersuchung, einem 12-Kanal-Elektrokardiogramm (EKG) und einem Ausbelastungstest auf dem Fahrradergometer unterzogen. Das Belastungstestprotokoll für männliche Athleten begann mit einer Last von 100 W, weibliche Athleten begannen mit 75 W. Die Last wurde alle 2 Minuten erhöht, um 50 W bei männlichen Athleten und um 25 W bei weiblichen Athleten. Der brachiale Blutdruck wurde automatisiert einmal pro Minute während der Test- und Erholungsphase gemessen. Zur Indexierung des systolischen Blutdruckanstieges in Bezug auf die Arbeitslast wurden hierbei entsprechend der Publikation von Hedman et al.[15] der SBP/W-slope und die peak SBP/W-ratio errechnet. Zudem wurde der SBP/MET-slope analog zur Originalpublikation[9] und unseren vorhergehenden Untersuchungen bestimmt. Die zentralen hämodynamischen Parameter und die vaskuläre Funktion wurden auf Basis der Pulswellenanalyse mit einem validierten oszillometrischen Verfahren gemessen.

Männliche Athleten waren größer (188,6 ± 7,2 vs. 167,1 ± 4,8 cm, p < 0,001), schwerer (90,9 ± 12,3 vs. 60,8 ± 7,7 kg, p < 0,001), hatten einen größeren Body-Mass-Index (25,5 ± 2,4 vs. 21,7 ± 1,9 kg/m^2, p < 0,001) und eine größere Körperoberfläche (2,18 ± 0,17 vs. 1,68 ± 0,11 m^2, p < 0,001) als weibliche Athleten. Darüber hinaus war bei den Sportlern die Trainingszeit pro Woche höher als bei den Sportlerinnen (17,85 ± 2,9 vs. 10,8 ± 2 Stunden/Woche, p < 0,001).

	Männliche Athleten (n = 47)	Weibliche Athleten (n = 25)	p
Herzfrequenz in Ruhe (/min)	57,2 ± 10,2	61,9 ± 10,2	0,068
Systolischer Blutdruck (mmHg)	124,8 ± 9,9	119,6 ± 11,1	0,057
Diastolischer Blutdruck (mmHg)	75,7 ± 7,3	73,5 ± 8,4	0,284
Zentraler systolischer Blutdruck (mmHg)	97,7 ± 8,3	95,7 ± 8,5	0,34
Zentraler diastolischer Blutdruck (mmHg)	57,2 ± 9,5	66,6 ± 9,5	*< 0,001*
Zentraler Pulsdruck in Ruhe (mmHg)	37,2 ± 6,5	28,9 ± 4,7	*< 0,001*
Mittlerer zentraler Blutdruck (mmHg)	72,4 ± 8,9	79,3 ± 8,9	*0,003*
Pulswellengeschwindigkeit (m/s)	6,2 ± 0,85	5,9 ± 0,58	0,079
Augmentationsindex@75 (%)	-20,7 ± 11	-17,4 ± 9,6	0,203
Resistance Index	16,15 ± 6,5	12,7 ± 10,7	0,148
Totaler peripherer Widerstand (dyn*s/cm^{-5})	1293 ± 317,5	1218 ± 341	0,369
Maximale Herzfrequenz (/min)	179,3 ± 11,8	183,5 ± 7,8	0,079
Maximaler systolischer Blutdruck (mmHg)	202,4 ± 19,6	177,1 ± 15,1	*< 0,001*
Maximale Watt (W)	342 ± 71,5	190 ± 31,5	*< 0,001*
Δ systolischer Blutdruck (mmHg)	77,6 ± 19,3	57,8 ± 14	*< 0,001*
Leistung (W/kg)	3,82 ± 0,92	3,17 ± 0,64	*< 0,001*
SBP/MET-slope (mmHg/MET)	5,7 ± 1,84	5,1 ± 1,6	0,158
SBP/Watt-slope (mmHg/W)	0,34 ± 0,12	0,53 ± 0,19	*< 0,001*
Peak SBP/Watt-ratio (mmHg/W)	0,61 ± 0,12	0,95 ± 0,17	*< 0,001*

Tabelle 5: Vergleich der vaskulären Funktionsanalyse, der Ergebnisse des Ausbelastungstestes und der neuen Arbeitslast-indexierten Parameter der Blutdruckantwort zwischen männlichen und weiblichen Athleten.

In der vaskulären Funktionsanalyse in Ruhe ergaben sich keine Unterschiede in den Markern der arteriellen Gefäßsteifigkeit Aix@75 und PWV zwischen männlichen und weiblichen Athleten. Frauen wiesen einen höheren zentralen diastolischen Blutdruck und einen niedrigeren zentralen Pulsdruck als Männer auf. Allerdings korrelierte keiner der gemessenen vaskulären Parameter mit dem Geschlecht ($p > 0,05$).
Bei männlichen Athleten korrelierte der brachiale systolische Blutdruck positiv mit der peak SBP/W-ratio. Ferner ergab sich eine signifikante negative Korrelation des brachialen diastolischen Blutdruckes mit dem SBP/W-slope. Alle anderen vaskulären Funktionsparameter korrelierten sowohl bei männlichen als auch bei weiblichen Athleten nicht signifikant mit den Arbeitslast-indexierten Parametern der Blutdruckantwort.

Interessanterweise konnten wir jedoch signifikante geschlechtsspezifische Unterschiede der Arbeitslast-indexierten Parameter der Blutdruckantwort feststellen. Bei männlichen Athleten war der SBP/W-slope ($0,34 \pm 0,12$ vs. $0,53 \pm 0,19$ mmHg/W, $p < 0,001$) und die peak SBP/W-ratio ($0,61 \pm 0,12$ vs. $0,95 \pm 0,17$ mmHg/W, $p < 0,001$) signifikant niedriger als bei weiblichen Athleten. Der SBP/MET-slope unterschied sich aber nicht zwischen Männern und Frauen ($5,7 \pm 1,84$ vs. $5,1 \pm 1,6$ mmHg/MET, $p = 0,158$) *(Tabelle 5)*. In den multivariaten Regressionsanalysen waren die vaskulären Funktionsparameter bei beiden Geschlechtern nicht in der Lage, die Blutdruckantwort vorherzusagen, und keiner der vaskulären Funktionsparameter in Ruhe erwies sich als unabhängiger Prädiktor der jeweiligen Arbeitslast-indexierten Parameter der Blutdruckantwort.

Eine wichtige Erkenntnis dieser Studie war, dass bei Leistungssportlern geschlechtsspezifische Unterschiede im SBP/W-slope und der peak SBP/W-ratio existieren, wohingegen der SBP/MET-slope keine Unterschiede zwischen männlichen und weiblichen Athleten aufwies. Keiner der in Ruhe gemessenen zentralen hämodynamischen Parameter oder vaskulären Funktionsparameter konnte diese geschlechtsspezifischen Unterschiede voraussagen. Trotz signifikant höherer maximaler systolischer Blutdruckwerte bei Sportlern waren sowohl der SBP/W-slope als auch die peak SBP/W-ratio bei Sportlerinnen höher. Dies deckt sich mit den Beobachtungen von Hedman et al.[15] und impliziert eine unterschiedliche Blutdruckregulation bei Belastung zwischen Männern und Frauen. Allerdings lagen einerseits die bei unseren Sportlerinnen ermittelten Werte für den SBP/W-slope ($0,53 \pm 0,19$ vs. $0,38 \pm 0,14$ mmHg/W) deutlich oberhalb der publizierten Referenzwerte für die Alterskohorte, andererseits lag die peak SBP/W-ratio ($0,95 \pm 0,17$ vs. $1,01 \pm 0,17$ mmHg/W)

darunter. Dies spricht dafür, dass diese Werte bei Frauen vom individuellen Fitnesszustand beeinflusst werden und weibliche Athleten aus diesem Grund andere Referenzwerte als die Normalbevölkerung benötigen.

Zusammenfassend konnten wir in unserer Studie geschlechtsspezifische Unterschiede der neuen Parameter SBP/W-slope und peak SBP/W-ratio nachweisen, wobei Frauen einen steileren Blutdruckanstieg aufwiesen. Im Gegensatz dazu konnten wir den SBP/MET-slope als geschlechtsunabhängigen Parameter für die Arbeitslast-indexierte Blutdruckantwort identifizieren. Da dieser zudem vergleichbar mit den publizierten Referenzwerten der Normalbevölkerung war, kann er problemlos zur Beurteilung der Blutdruckantwort bei einer Sporttauglichkeitsuntersuchung bei Männern und Frauen verwendet werden. Aufgrund der stärkeren Abweichungen zu den alters- und geschlechtsspezifischen Referenzwerten müssen jedoch für die peak SBP/W-ratio bei Athleten eigene Referenzwerte etabliert werden. Bei Frauen ist dies zudem für den SBP/W-slope notwendig, der offensichtlich stärker von der körperlichen Fitness beeinflusst wird.

5. Diskussion

Die in unseren Studien untersuchten Leistungssportler zeichnen sich durch eine hohe und homogene körperliche Fitness aus, was einen deutlichen Unterschied zu Normalpopulationen darstellt, bei denen sich typischerweise ein breites Spektrum der körperlichen Aktivität und körperlichen Fitness findet. Aufgrund der anerkannten und therapeutisch genutzten Effekte einer sportlichen Aktivität auf den Blutdruck[6], bietet sich daher gerade in diesen Studienpopulationen die Chance, die Korrelation zwischen Hämodynamik, Blutdruckregulation und Leistungsfähigkeit unter Einbeziehung einer weiteren Variable unabhängig vom Einfluss der körperlichen Fitness zu beleuchten.

Der Einfluss von Vitamin D auf die körperliche Leistungsfähigkeit, Verletzungshäufigkeit[64] und kardiovaskuläre Gesundheit[45, 46, 54] wird seit Jahren intensiv erforscht[48, 49, 56]. Bisherige Studienergebnisse assoziierten einen Vitamin-D-Mangel mit einer eingeschränkten Leistungsfähigkeit bei Athleten[48]. Allerdings ist die Datenlage bezüglich der Verbesserung der Leistungsfähigkeit durch eine Supplementierung uneindeutig[48]. Ein Grund hierfür ist sicherlich, dass die anzustrebenden optimalen Vitamin-D-Spiegel sowohl für die Normalbevölkerung als auch für Athleten derzeit wissenschaftlich umstritten sind[48, 54, 58-61] und es zudem unterschiedliche Definitionen eines Vitamin-D-Mangels gibt[48, 59]. Weitestgehende Einigkeit besteht jedoch aktuell darin, dass der Vitamin-D-Status einer Person mit Hilfe des zirkulierenden 25-OH-Vitamin D bestimmt wird[47].
Da Konzentrationen über 30 ng/ml das Risiko für Knochenmineralisationsdefekte minimieren[62], definierten wir in unseren Studien, wie auch andere Arbeitsgruppen[63, 64], 25-OH-Vitamin-D-Spiegel < 30 ng/ml als insuffiziente Vitamin-D-Spiegel.

Die von uns erstmalig beschriebene hohe Prävalenz (44,3%) eines Vitamin-D-Mangels bei professionellen Handballspielern in Deutschland ist vergleichbar mit dem Resultat einer anderen Studie, die polnische Leistungssportler untersuchte[92]. In Abhängigkeit von der Jahreszeit, der geographischen Region und der untersuchten Kollektive finden sich in der Literatur unterschiedliche Prävalenzen eines Vitamin-D-Mangels [48, 66, 92]. Zudem wurde über ein höheres Risiko eines Vitamin-D-Mangels bei Hallensportlern berichtet[92].
Die klinische Relevanz unseres Studienergebnisses spiegelt sich in der kürzlich nachgewiesenen Reduktion von Stressfrakturen durch eine Vitamin-D-Supplementation bei Athleten mit insuffizienten Vitamin-D-Spiegeln (< 30 ng/ml) wider[64]. Zudem wurde eine

Erhöhung des Parathormons als Risikofaktor für Stressfrakturen identifiziert[93]. Da diese auch in unserer Athleten mit Vitamin-D-Mangel detektierbar war, wird durch unsere Ergebnisse der definierte untere Grenzwert von 30 ng/ml 25-OH-Vitamin D zur Erhaltung der Knochengesundheit bei Athleten gestärkt.
Eine Überwachung des Vitamin-D-Status bei Leistungssportlern in Deutschland erscheint daher sinnvoll, insbesondere in den Wintermonaten[92]. Ferner sollten präventive Strategien zur Vermeidung eines Vitamin-D-Mangels erarbeitet werden und, im Falle eines Mangels, eine Supplementierung mit Vitamin D vorgenommen werden, um Stressfrakturen mit konsekutiven langen Ausfallzeiten der Athleten zu vermeiden.

Ob der für die Skelettgesundheit bei Athleten definierte untere Grenzwert von 30 ng/ml 25-OH-Vitamin D auch für die Erhaltung der kardiovaskulären Gesundheit und eine optimale körperliche Leistungsfähigkeit bei Leistungssportlern gilt, ist gegenwärtig unklar. Bisherige Studien zu blutdrucksenkenden Wirkungen einer Vitamin-D-Supplementierung in Normalpopulationen[75-77] erbrachten widersprüchliche Ergebnisse. Allerdings blieb auch hier zumeist der Fitnessstatus[43, 44] unberücksichtigt. Entsprechende Untersuchungen bei Athleten fehlen bisher gänzlich.
Mit Hilfe validierter nichtinvasiver Messmethoden[26, 28] können die anerkannten Wirkungen von Vitamin D auf die Gefäßfunktion[74] in Untersuchungen miteinbezogen werden und somit Auswirkungen eines Vitamin-D-Mangels früh und sensitiv erfasst werden. Ferner kann mit diesen Methoden der cBP, der dem brachialen Blutdruck bei der Identifizierung von Veränderungen der vaskulären Funktionsparameter[94] und des kardiovaskulären Risikos[19, 20, 25, 95] überlegen ist, valide gemessen werden[28].
In unserer Kohorte männlicher Leistungssportler konnten wir zum ersten Mal zeigen, dass der cBP von Athleten mit insuffizienten Vitamin-D-Werten im Bereich der altersentsprechenden Normalbevölkerung[25] lag, während suffiziente Vitamin-D-Werte mit einem niedrigeren zentralen Blutdruck assoziiert waren. Unsere Beobachtung eines signifikant erhöhten diastolischen cBP bei Athleten mit Vitamin-D-Mangel impliziert eine Beeinflussung des Tonus der peripheren Widerstandsgefäße durch Vitamin D, was bereits in anderen Studien gezeigt wurde[72, 73]. Trotzdem ergaben sich keine messbaren Unterschiede in den Markern der vaskulären Funktion wie PWV und Aix@75. Diese Parameter waren in beiden Gruppen vergleichbar mit den Ergebnissen anderer Studien, die Athleten untersuchten[31, 36] und niedriger als bei gesunden Nicht-Athleten[38].

Zusammenfassend konnte daher in unserer Untersuchung ein höherer brachialer und zentraler Blutdruck bei Athleten mit Vitamin-D-Mangel detektiert werden. Trotzdem lagen die anerkannten Parameter der Gefäßfunktion im Normbereich und unterschieden sich zwischen den Gruppen nicht. Somit scheint die durch den Vitamin-D-Mangel induzierte Erhöhung des Gefäßtonus der Widerstandsgefäße in Ruhe durch eine verbesserte periphere Gefäßfunktion ausgeglichen zu werden, so dass keine messbare Zunahme der Gefäßsteifigkeit resultiert. Man könnte daher einen kompensatorischen Effekt der hohen körperlichen Fitness unserer Athleten auf die kardiovaskulären Auswirkungen eines Vitamin-D-Mangels vermuten. Der durch die Fitness herbeigeführte hämodynamische Vorteil scheint sich bei suffizienten Vitamin-D-Spiegeln in Form einer Reduktion des cBP widerzuspiegeln und bei insuffizientem Vitamin-D-Spiegel verloren zu gehen. Allerdings sollte diese Hypothese in weiteren Studien überprüft werden. Einschränkend muss zudem erwähnt werden, dass unsere Pilotstudie nur wenige männliche Athleten umfasste, die lediglich zu einem Messzeitpunkt untersucht wurden.

Wir nahmen an, dass sich die in Ruhe bei Leistungssportlern noch kompensierte Einschränkung der vaskulären Funktion als Folge eines 25-OH-Vitamin-D-Mangels unter einer maximalen Belastung in Form einer gesteigerten Blutdruckantwort demaskiert. Allerdings zeigte unsere durchgeführte Studie, dass der Vitamin-D-Spiegel nicht mit der belastungsinduzierten Blutrucksteigerung und dem maximalen systolischen brachialen Blutdruck bei einer standardisierten ergometrischen Untersuchung korreliert. Dies deckt sich mit den Ergebnissen von Zaleski[78], der dies in der Normalbevölkerung untersucht hatte.
Athleten mit suffizienten Vitamin-D-Spiegeln wiesen einen höheren maximalen systolischen Blutdruck und einen höheren Pulsdruck als Athleten mit insuffizienten Vitamin-D-Spiegeln auf, allerdings unterschied sich die individuelle Blutdruckantwort nicht. Vergleiche mit anderen Studien, welche die Blutdruckregulation von Leistungssportlern bei einem ergometrischen Ausbelastungstest untersuchten, berichteten sowohl über niedrigere als auch höhere maximale systolische Blutdruckwerte[11, 79]. In keiner dieser Studien wurde der Vitamin-D-Status der Athleten erhoben, was die Vergleichbarkeit der Ergebnisse einschränkt.

Interessanterweise konnten wir eine hochsignifikante Korrelation zwischen höheren Vitamin-D-Spiegeln und einer besseren Leistungsfähigkeit in unserer Studienkohorte identifizieren. Der höhere maximale systolische Blutdruck bei Sportlern mit suffizienten 25-OH-Vitamin-D-Spiegeln war Ausdruck der besseren Leistungsfähigkeit dieser Gruppe. Durch die Indexierung

der maximalen systolischen Blutdruckwerte auf die individuelle Leistungsfähigkeit konnten wir aufzeigen, dass die individuelle Blutdruckantwort zwischen Athleten mit insuffizienten und suffizienten Vitamin-D-Spiegeln nicht unterschiedlich war.

Daher scheinen die Folgen eines Vitamin-D-Mangels auf die Blutdruckregulation unter Belastung durch vaskuläre Funktionsanpassungen kompensiert werden zu können. Allerdings sind die exakten Wirkungen von Vitamin D auf die Gefäßzellfunktion, Kardiomyozyten und Arterienfunktion in verschiedenen Regionen des menschlichen Gefäßsystems bisher noch unklar[48, 78]. Einschränkend muss zudem darauf hingewiesen werden, dass in unseren Untersuchungen keine Möglichkeit der nichtinvasiven Messung der zentralen Hämodynamik unter Belastungsbedingungen bestand und deswegen nur die weniger sensitiven brachialen Blutdruckwerte genutzt werden konnten. Dies liegt an der oszillometrischen Messmethodik, die in Ruhe valide Ergebnisse liefern kann, allerdings nicht während eines Belastungstestes [26].

Zusammenfassend konnten wir durch unsere Studien zu Vitamin D bei Leistungssportlern klinisch relevante neue Erkenntnisse gewinnen. Zum einen stützen unsere Ergebnisse die untere Schwelle von 30 ng/ml 25-OH-Vitamin D zur Erhaltung der Skelettgesundheit und zur Prophylaxe von Stressfrakturen bei Athleten. Daher sollte ein Monitoring des Vitamin-D-Spiegels stattfinden und beim Auftreten eines Vitamin-D-Mangels eine Substitution vorgenommen werden. Zum anderen wiesen wir nach, dass sich ein Vitamin-D-Mangel auf die vaskuläre Funktion und die zentrale Hämodynamik auswirkt. Diese Folgen können allerdings durch eine hohe körperliche Fitness insoweit kompensiert werden, dass keine relevante Erhöhung der individuellen Blutdruckantwort unter Belastung auftritt, was wir mit Hilfe der Arbeitslastindexierung aufzeigen konnten. Allerdings deuten unsere Studienergebnisse darauf hin, dass ein Vitamin-D-Mangel zu einer eingeschränkten Leistungsfähigkeit bei Athleten führt. Ob dies über die muskuloskelettalen oder kardiovaskulären Wirkungen von Vitamin D vermittelt wird, welche 25-OH-Vitamin-D-Werte für eine optimale Leistungsfähigkeit nötig sind und ob ein Anheben der Vitamin-D-Spiegel die Leistungsfähigkeit steigert, ist jedoch unklar und sollte in weiteren prospektiven Studien untersucht werden.

Der Einfluss einer körperlichen Aktivität auf die vaskuläre Funktion ist bereits länger Gegenstand wissenschaftlicher Untersuchungen[80, 81, 96]. Zur Auswirkung einer intensiven Sportausübung auf die vaskuläre Funktion und den cBP existieren gegenwärtig uneinheitliche Studienergebnisse. Einserseits wurden eine erhöhte arterielle Steifigkeit[30-32] und ein erhöhter cBP[30] bei Athleten beschrieben, andererseits wurden genau gegenteilige Effekte[33-35] oder keine Effekte[36] beobachtet. Die funktionellen und strukturellen kardiovaskulären Adaptationen infolge einer gesteigerten körperlichen Aktivität scheinen jedoch abhängig von der Art und Intensität der sportlichen Belastung zu sein und zudem eine wichtige Rolle für die Leistungsfähigkeit von Athleten zu spielen[31, 37, 80, 97, 98].

So konnten Denham et al.[97] in ihrer Studie zeigen, dass der Aix@75, nicht jedoch cBP oder PWV, bei Ausdauersportlern invers mit der maximalen Sauerstoffaufnahme korreliert war. Diese erwies sich hierbei als unabhängiger Prädiktor für Aix@75. Daraus schlossen die Autoren, dass Aix@75 eine Rolle bei der kardiorespiratorischen Fitness von Ausdauersportlern spielt[97]. Interessanterweise liessen sich diese Erkenntnisse auch bei gesunden männlichen Kontrollpersonen unserer Studie nachweisen, wobei der Aix@75 und die VO2 max. als Prädiktoren der Leistungsfähigkeit (W/kg) bei einer ausbelastenden Ergometrie fungierten.

Hingegen waren diese Assoziationen bei unseren untersuchten Leistungssportlern nicht nachweisbar. Erklärbar ist dies am ehesten über die Studienkohorte, die bei uns jünger im Vergleich zu Denham et al.[97] war und zudem eine andere Sportart ausübte[6]. Zudem weist der niedrige Trainingsumfang der untersuchten Ausdauerathleten bei Denham et al.[97] die Studienteilnehmer eher als Freizeitathleten aus. Hingegen wurden in unseren Studien Leistungssportler untersucht, bei denen der in Ruhe gemessene Aix@75 für die Prädiktion der Leistungsfähigkeit Limitationen aufzuweisen scheint, was ebenfalls von anderen Arbeitsgruppen berichtet wurde[99].

Jedoch konnten wir bei Leistungssportlern, aber nicht bei den Kontrollpersonen, eine signifikante inverse Korrelation zwischen Widerstandsindex (R) und Leistungsfähigkeit detektieren, wobei hier R und die VO2 max. als unabhängige Prädiktoren der Leistungsfähigkeit zu identifizieren waren. Die inverse Korrelation zwischen Widerstandsindex, als Mass für den globalen peripheren Widerstand, und höherer Leistungsfähigkeit bei Athleten in unserer Studie unterstreicht den Zusammenhang zwischen Gefäßfunktion, Blutdruckregulation und Leistungsfähigkeit. Dies stimmt auch mit den Untersuchungen von Green et al.[80, 81] überein, bei denen der peripher-vaskuläre Widerstand

als wichtige Komponente sowohl der Blutdruckregulation als auch der Leistungsfähigkeit erkannt wurde.
Ferner lassen unsere Ergebnisse vermuten, dass bei Leistungssportlern Unterschiede der kardiovaskulären Funktion erst unter Belastungsbedingungen apparent werden und dann zu einer unterschiedlichen Blutdruckregulation und Leistungsfähigkeit führen. Bei Leistungssportlern können selbst leichtgradige kardiovaskuläre Funktionseinschränkungen die Leistungsfähigkeit vermindern, den Blutdruck unter Belastung erhöhen und damit langfristig zu schwerwiegenden gesundheitlichen Folgen führen[12].

Die in Europa für kompetitive Athleten vorgeschriebene Sporttauglichkeitsuntersuchung[6] bietet die Möglichkeit zur frühzeitigen Detektion kardiovaskulärer Funktionseinschränkungen. Deren wesentlicher Bestandteil ist eine Belastungsuntersuchung, die vorwiegend in Form eines Belastungs-EKGs ohne oder mit gleichzeitiger Atemgasanalyse durchgeführt wird[6]. Daher erscheint eine klare Einordnung, wann eine normale Blutdruckantwort beim Ausbelastungstest vorliegt und wann nicht, zwingend erforderlich. Allerdings existieren aktuell weder für Normalpopulationen noch für Athleten Normwerte für das Blutdruckverhalten unter Belastung[2], was auf diskrepante Studienergebnisse[8-10] zu diesem Thema zurückzuführen ist. Diese Unklarheit bezüglich eines normalen Blutdruckverhaltens unter Belastung[2] stellt insbesondere bei der Evaluation von Athleten im Rahmen der Sporttauglichkeitsuntersuchung[6] ein Problem dar. Aufgrund der physiologisch nahezu linearen Beziehung zwischen systolischem Blutdruck und steigender Arbeitslast werden insbesondere bei Individuen mit hoher körperlicher Fitness höhere maximale Blutdruckwerte erreicht[100].
Die klinische Bedeutung einer überschießenden Blutdruckreaktion für Athleten wurde bereits mehrfach untersucht und ein erhöhtes Risiko für die Entwicklung einer arteriellen Hypertonie[12, 101], einer linksventrikulären Hypertrophie sowie einer myokardialen Fibrosierung[102] postuliert. Allerdings divergierten die Definitionen einer überschießenden Blutdruckreaktion in den Studien. So sind bis heute keine klaren Grenzen der normalen Blutdruckantwort bei Athleten definiert[2], was unter anderem an der bisherigen Vorgehensweise der Orientierung an Absolutwerten liegt[103].
Erstmalig findet sich nun jedoch in den neu erschienenen europäischen sportkardiologischen Leitlinien aus dem Jahr 2020 der Hinweis, dass bei einem systolischen Blutdruck > 200 mmHg bei 100 Watt Belastung, bei in Ruhe normotensiven Blutdruckwerten, eine weiterführende klinische Evaluation stattfinden sollte, um kardiovaskuläre Pathologien

auszuschließen[6]. Diese Neuerung, dass der erreichte systolische Blutdruckwert auf die jeweilige Belastung indexiert betrachtet wird, hilft insbesondere bei der Beurteilung der belastungsinduzierten Blutdruckantwort von körperlich fitten Individuen[100]. Hierauf aufbauend entwickelten Hedman und Kollegen[9] einen Index, der die systolische Blutdruckantwort bei einem Belastungstest auf das geleistete metabolische Äquivalent bezieht, den SBP/MET-slope. Dieser war in der untersuchten männlichen Patientenkohorte den maximal erreichten systolischen Blutdruckwerten in der Vorhersage der Sterblichkeit überlegen, wobei ein höherer SBP/MET-slope mit einem höheren Sterblichkeitsrisiko verbunden war[9]. In einer weiteren Publikation definierten Hedman und Kollegen[15] alters- und geschlechtsspezifische Normwerte für eine Arbeitslast-indexierte Betrachtung der Blutdruckantwort bei einem Fahrradergometertest und führten zwei weitere Arbeitslast-indexierte Parameter zur Beurteilung des Blutdruckverhaltens unter Belastung ein, den SBP/Watt-slope und die peak SBP/W-ratio.

In Anbetracht dieser neuen Daten untersuchten wir erstmalig die Anwendbarkeit des SBP/MET-slopes in eine Kohorte männlicher Leistungssportler und verglichen ihn mit der individuellen Leistungsfähigkeit. Die Berechnung des SBP/MET-slopes und die Einteilung in die entsprechenden Quartile nahmen wir analog zur Originalpublikation vor[9].
In der gesamten Studienpopulation detektierten wir einen mittleren SBP/MET-slope von 5,4 ± 1,7 mmHg/MET und einem maximalen SBP/MET-slope von 8,8 mmHg/MET. Diese Werte decken sich mit den Beobachtungen von Hedman et al.[9], die bei ihren Patienten mit einem niedrigen Ausgangsrisiko den Mittelwert des SBP/MET-slope mit 5 mmHg/MET und die 95-%-Perzentile mit 10 mmHg/MET und in der Gesamtkohorte einen Median von 6,4 mmHg/MET wiedergeben[9].
Interessanterweise konnten wir zwischen den SBP/MET-slope Quartilen hochsignifikante Unterschiede in den maximalen systolischen Blutdruckwerten, im systolischen Blutdruckanstieg sowie in der Leistungsfähigkeit detektieren. So wies die Gruppe mit einem SBP/MET-slope < 4,3 mmHg/MET signifikant niedrigere maximale systolische Blutdruckwerte auf, besaß allerdings gleichzeitig eine signifikant höhere Leistungsfähigkeit als die anderen Gruppen.
Ähnliche Beobachtungen machte eine Studie, welche die Auswirkungen des Blutdruckes in Ruhe auf die Leistungsfähigkeit (VO2 max.) bei Leistungssportlern untersuchte[82]. Darin war bereits bei einem systolischem Ruheblutdruck > 130 mmHg eine schlechtere Leistungsfähigkeit und ein höherer maximaler systolischer Blutdruck im Vergleich zu einem

systolischen Ruheblutdruck < 130 mmHg nachweisbar[82]. Dies verdeutlicht den Zusammenhang zwischen Blutdruckregulation unter Belastung und Leistungsfähigkeit bei Athleten.
Daher ist es nicht überraschend, dass unsere Kohorte im Vergleich zu anderen Studien einerseits höhere[11], andererseits niedrigere maximale systolische Blutdruckwerte[79] aufwies und gleichzeitig relevante Unterschiede in der Leistungsfähigkeit der Studienteilnehmer imponierten. Da in den anderen Studien keine Indexierung der Blutdruckantwort auf die Arbeitslast vorgenommen wurde, waren keine direkten Vergleiche mit dem SBP/MET-slope möglich. Allerdings wird wiederum deutlich, dass die Arbeitslast-indexierte Analytik der Blutdruckregulation unter Belastung bei Leistungssportlern Vorteile gegenüber der Betrachtung der maximalen systolischen Blutdruckwerte hat.

Unsere Untersuchung des SBP/MET-slopes bei männlichen Leistungssportlern zeigt, dass er auch in diesen Kohorten herangezogen werden kann, um eine Charakterisierung der Blutdruckantwort vorzunehmen. Zudem weisen sowohl unsere als auch die Ergebnisse von Hedman et al.[9] darauf hin, dass der als normal vorgeschlagene SBP/MET-slope von 10 mmHg/MET[13] keineswegs eine normale Blutdruckantwort widerspiegelt, sondern allenfalls als oberes Limit angesehen werden kann. Daher könnte der SBP/MET-slope dazu beitragen, zukünftig Athleten mit einer überschießenden Blutdruckregulation während eines Ausbelastungstestes im Rahmen einer Sporttauglichkeitsuntersuchung zu identifizieren. Darüber hinaus war ein höherer SBP/MET-slope mit einer niedrigeren Leistungsfähigkeit assoziiert, was eine Beeinträchtigung der sportlichen Leistung bedeuten kann. Natürlich müssen in der Zukunft noch valide Grenzkorridore für den SBP/MET-slope bei Sportlern etabliert werden und die prognostische Relevanz in prospektiven Studien überprüft werden. Allerdings erscheint die Einteilung anhand des SBP/MET-slopes, insbesondere vor dem Hintergrund der prognoserelevanten Daten von Hedman et al.[9], vielversprechend.

Das erste klinische Korrelat einer subklinischen vaskulären Funktionseinschränkung kann bei in Ruhe normotensiven Menschen eine überschießende Blutdruckregulation unter Belastungbedingungen sein[39, 100, 104]. In einer kürzlich veröffentlichten Studie mit gesunden jungen Teilnehmern beider Geschlechter (Alter 37 ± 5 Jahre) konnte gezeigt werden, dass die in Ruhe gemessene PWV eine überschießende Blutdruckantwort voraussagen kann[38]. Hieraus wurde gefolgert, dass die vaskuläre Funktionsanalyse dazu beitragen könnte, eine bessere

kardiovaskuläre Risikoeinschätzung insbesondere bei jungen und ansonsten gesunden Menschen zu erreichen[39, 40].
Nachdem wir bestätigten, dass der SBP/MET-slope auch bei männlichen Leistungssportlern anwendbar ist, wollten wir daher im nächsten Schritt den Zusammenhang zwischen der vaskulären Funktion und den neu eingeführten Arbeitslast-indexierten Parametern der Blutdruckantwort untersuchen sowie potentielle Unterschiede zwischen Athleten und Nicht-Athleten evaluieren.

Auch in dieser Untersuchung zeigte sich, dass die maximalen systolischen Blutdruckwerte für die klinische Beurteilung der individuellen Blutdruckregulation nicht geeignet sind. Zwischen Athleten und Kontrollpersonen waren diese nicht unterschiedlich, obwohl Athleten eine signifikant bessere Leistungsfähigkeit aufwiesen.
Hingegen waren die Werte der Arbeitslast-indexierten Parameter der Blutdruckantwort bei Athleten durchweg niedriger als bei den Kontrollen. Im Vergleich zu den publizierten Referenzwerten der Altersgruppe[15] fiel bei den untersuchten Leistungssportlern auf, dass der SBP/MET-slope und der SBP/W-slope vergleichbare Werte aufweisen, wohingegen die peak SBP/W-ratio deutlich niedriger lag.
Dies deutet darauf hin, dass die peak SBP/W-ratio relevant durch den Fitnesszustand beeinflusst wird. Demzufolge scheinen Leistungssportler, aufgrund der höheren erreichten maximalen Wattwerte, niedrigere Normwerte für diesen Parameter zu benötigen. Daher ist die peak SBP/W-ratio in athletischen Populationen nicht in gleicher Weise zu verwenden wie in Normalpopulationen. Hingegen scheinen der SBP/MET-slope und der SBP/W-slope weniger durch die körperliche Fitness beeinflusst zu sein.
Zudem bestätigte sich in unserer Studie die Annahme, dass der vorgeschlagene normale SBP/MET-slope von 10 mmHg/MET[13] allenfalls als oberer Grenzwert angesehen werden kann. So lag die 95-%-Perzentile bei Athleten bei 9,4 mmHg/MET und bei Kontrollen bei 10,3 mmHg/MET.

Erwartungsgemäß zeigten sich signifikante Unterschiede der zentralen Hämodynamik und der vaskulären Funktionsparamter zwischen Athleten und Kontrollen bereits in Ruhe, wobei jedoch keine Unterschiede des Widerstandsindex und des totalen peripheren Widerstandes gemessen wurden. Die ermittelten Werte für die PWV und den cBP waren vergleichbar mit unseren vorangegeangenen Studien und denen anderer Studien, die Athleten[30, 31, 35, 37] und Normalpopulationen[25] untersuchten. Trotz der Unterschiede der vaskulären Funktion

zwischen Leistungssportlern und Kontrollgruppe korrelierte keiner der in Ruhe erhobenen vaskulären Funktionsparameter mit den Arbeitslast-indexierten Parametern der Blutdruckantwort. Demzufolge war es auch nicht möglich, die individuelle Blutdruckantwort anhand der in Ruhe gemessenen vaskulären Werte vorauszusagen. Dies steht im Widerspruch zu einer Studie, die eine überschießende Blutdruckantwort bei jungen Menschen mit einer erhöhten PWV assoziierte[38]. Allerdings wurden in dieser keine Athleten untersucht, die typischerweise eine höhere arterielle vasodilatatorische Reserve aufweisen. Zudem wurden die Ergebnisse nicht nach Geschlechtern aufgeteilt berichtet und die Definition der überschießenden Blutdruckantwort wurde nur anhand der absoluten maximalen systolischen Blutdruckwerte vorgenommen[38]. Darüber können die unterschiedlichen Ergebnisse ausreichend erklärt werden.

Dass insbesondere unter Belastungsbedingungen Unterschiede der vaskulären Funktion zwischen Athleten und Kontrollen bestehen, wird bei der Betrachtung der Blutdruckveränderungen bei steigender Belastung deutlich. Bei jeder Belastungsstufe wiesen die Athleten einen niedrigeren systolischen Blutdruckwert auf und die Kurve der Blutdruckantwort schien im Vergleich zu den Kontrollprobanden nach rechts verschoben zu sein. Allerdings unterschied sich der maximale systolische Blutdruck zwischen beiden Gruppen nicht. Hingegen imponierten bei prozentualer Indexierung der Blutdruckwerte auf die individuell erreichte maximale Wattzahl nahezu deckungsgleiche Kurven bei Athleten und Kontrollen. Dies unterstreicht den Zusammenhang zwischen Blutdruckregulation, individueller Leistungsfähigkeit und vaskulärer Funktion unter Belastung, der durch vaskuläre Funktionsmessungen in Ruhe bei Leistungssportlern nicht erfasst werden kann. Zudem wird die sinnvolle Anwendung der neuen Parameter SBP/MET-slope und SBP/W-slope auch für männliche Athleten bestätigt.

Bemerkenswerterweise waren die angegebenen Normwerte für diese neu eingeführten Arbeitslast-indexierten Parameter der Blutdruckantwort bei Frauen deutlich höher als bei Männern, was auf einen steileren Anstieg des Blutdruckes während der Belastung hinweist[15]. Vor dem Hintergrund der bekannten divergierenden Blutdruckregulation in Ruhe zwischen Männern und Frauen[83-85] wurde angenommen, dass diese geschlechtsspezifischen Unterschiede wesentlich durch die Gefäßfunktion moduliert werden[15, 38, 84, 90, 91] und daher möglicherweise durch Messung der zentralen Hämodynamik und der vaskulären Funktion aufgedeckt werden können[15].

Inwieweit die neuen Arbeitslast-indexierten Parameter der Blutdruckantwort und die vaskuläre Funktion zwischen männlichen und weiblichen Leistungssportlern differieren und ob eine Übertragung der Ergebnisse aus der Normalpopulation für Leistungssportler möglich ist, untersuchten wir in einer weiteren Studie.

Wir konnten bei Leistungssportlern geschlechtsspezifische Unterschiede im SBP/W-slope und der peak SBP/W-ratio detektieren, wohingegen der SBP/MET-slope keine signifikanten Unterschiede zwischen männlichen und weiblichen Athleten aufwies. Zudem konnte keiner der in Ruhe gemessenen vaskulären Funktionsparameter diese geschlechtsspezifischen Unterschiede voraussagen. Dies deckt sich mit unserer vorhergehenden Untersuchung bei männlichen Athleten.

Im Einklang mit den publizierten Referenzwerten[15] waren sowohl der SBP/W-slope als auch die peak SBP/W-ratio bei Sportlerinnen höher. Allerdings lagen einerseits die bei unseren Sportlerinnen ermittelten Werte für den SBP/W-slope (0,53 ± 0,19 vs. 0,38 ± 0,14 mmHg/W) deutlich oberhalb der publizierten Referenzwerte für die weibliche Alterskohorte, andererseits lag die peak SBP/W-ratio (0,95 ± 0,17 vs. 1,01 ± 0,17 mmHg/W) darunter. Dies spricht dafür, dass diese Werte bei Frauen vom individuellen Fitnesszustand beeinflusst werden und weibliche Athleten aus diesem Grund andere Referenzwerte als die Normalbevölkerung benötigen.

Diese Beobachtung könnte darin begründet liegen, dass bei Frauen vor der Menopause die beta-adrenerge Empfindlichkeit im Vergleich zu Männern erhöht ist. Hierdurch wird die vasokonstriktorische Reaktion unter steigender Belastung aufgrund der gleichzeitigen beta-adrenergen vermittelten Vasodilatation[84, 105] abgeschwächt, was ebenfalls bei konstant durchgeführter submaximaler Belastung nachzuweisen war[106]. Bei den höchsten Belastungsintensitäten wird jedoch auch hier ein durch den sogenannten Muskel-Metaboreflex bedingter Anstieg des peripheren Widerstands beobachtet[86, 107], der bei Sportlerinnen im Vergleich zu untrainierten Frauen verändert zu sein scheint. Ein höherer SBP/W-slope bei trainierten Frauen kann daher Ausdruck eines höheren Fitnessniveaus und einer besseren Leistungsfähigkeit sein.

Im Gegensatz dazu ist die belastungsinduzierte Blutdruckantwort bei Männern durch eine Zunahme des Herzzeitvolumens und des gesamten peripheren Widerstands gekennzeichnet[105] und daher weniger vom Fitnessniveau beeinflusst. Aus diesem Grund waren die Werte unserer männlichen Athleten mit den vorgeschlagenen Referenzwerten[15] der Allgemeinbevölkerung vergleichbar (0,34 ± 0,12 gegenüber 0,33 ± 0,11 mmHg/W).

Diese ermittelten geschlechtsspezifischen Unterschiede, die sowohl bei trainierten als auch bei untrainierten Personen nachweisbar waren, deuten auf eine unterschiedliche Blutdruckregulation unter Belastung zwischen Männern und Frauen hin, die unabhängig vom Fitnessniveau besteht, komplex und noch nicht vollständig geklärt ist[84, 105].

Aufgrund der stärkeren Abweichungen zu den alters- und geschlechtsspezifischen Referenzwerten müssen daher für die peak SBP/W-ratio bei Athleten eigene Referenzwerte etabliert werden. Bei Athletinnen ist dies zudem für den SBP/W-slope notwendig, der hier offensichtlich stärker von der körperlichen Fitness beeinflusst wird. Hingegen konnten wir den SBP/MET-slope als geschlechtsunabhängigen Marker für die Arbeitslast-indexierte Blutdruckantwort identifizieren.

Zusammenfassend konnten wir mit unseren Studien erstmalig die neu eingeführten Arbeitslast-indexierten Parameter der Blutdruckantwort bei Leistungssportlern und deren Assoziation zur vaskulären Funktion untersuchen.
Hierbei konnten wir zeigen, dass bei männlichen Leistungssportlern der SBP/W-slope vergleichbar mit den publizierten Referenzwerten[15] war, wohingegen bei Leistungssportlerinnen deutliche Unterschiede bestanden. Zudem wiesen wir nach, dass die Referenzwerte für die peak SBP/W-ratio[15] sowohl bei männlichen als auch bei weiblichen Leistungssportlern nicht für die klinische Beurteilung der individuellen Blutdruckantwort geeignet sind.
Der SBP/MET-slope wurde als geschlechtsunabhängiger Marker identifiziert. Zudem waren die Werte vergleichbar mit den Normwerten der Alterskohorte, so dass dieser Parameter aktuell zur klinischen Beurteilung eines Ausbelastungstestes im Rahmen einer Sporttauglichkeitsuntersuchung geeignet scheint. Der als normal vorgeschlagene systolische Blutdruckanstieg von 10 mmHg/MET[13] sollte hierbei jedoch, nach den Ergebnissen unserer Studien, den oberen Grenzwert markieren.

Auch wenn bisher prognostische Daten für die Arbeitslast-indexierten Parameter der Blutdruckregulation bei Athleten fehlen, scheint der SBP/MET-slope aufgrund der bisherigen Untersuchungen[9] vielversprechend zu sein, um die Unklarheiten in der Beurteilung des Blutdruckverhaltens während eines Ausbelastungstestes im Rahmen einer Sporttauglichkeitsuntersuchung zu beseitigen.

In der Zunkunft sollten alters- und geschlechtsspezifische Referenzwerte für die Arbeitslast-indexierten Parameter bei Athleten definiert und die prognostische Relevanz der verschiedenen Parameter evaluiert werden.
In unseren Untersuchungen wurden nur in Ruhe normotensive Athleten untersucht und es ist anzunehmen, dass bei einer bestehenden Hypertension in Ruhe die Arbeitslast-indexierten Parameter nicht in gleicher Weise anwendbar sind, da sie auch wesentlich von der systolischen Blutdruckdifferenz (maximaler systolischer Blutdruck- systolischer Blutdruck in Ruhe) abhängen. Weiterhin erscheint es möglich, dass die Sportart und die Art des Ausbelastungstestes die Blutdruckantwort unter Belastung, und damit die Arbeitslast-indexierten Parameter, unterschiedlich beeinflussen.

Ferner konnten wir den Einfluss der vaskulären Funktion auf die Blutdruckregulation unter Belastung und auf die individuelle Leistungsfähigkeit bei Athleten nachweisen. Dabei gelang es bei Athleten nicht, durch eine vaskuläre Funktionsanalyse in Ruhe die individuelle Blutdruckantwort vorauszusagen. Leider war es mit der in unseren Studien genutzten validierten oszillometrischen Methode nicht möglich, die vaskuläre Funktion auch unter Belastungsbedingungen zu bestimmen. Dies liegt an Messtechnik, die zwar in Ruhe valide Ergebnisse liefert, allerdings nicht bei einem Ausbelastungstest[26, 108]. Nichtinvasive Methoden zur Messung der vaskulären Funktion unter Belastung befinden sich in der Entwicklung und können, nach entsprechender Validierung, daher vermutlich bald einen Beitrag leisten, um die Blutdruckantwort in verschiedenen Populationen zu charakterisieren und Referenzwerte zu etablieren.

Mit unseren Untersuchungen liefern wir erste Orientierungswerte für die Arbeitslast-indexierten Parameter der Blutdruckantwort bei Leistungssportlern und weisen auf den Zusammenhang zwischen Blutdruckregulation, vaskulärer Funktion und Leistungsfähigkeit hin. Zukünftig sollte das Ziel sein, das diagnostische Potential des regelhaft durchgeführten Ausbelastungstestes im Rahmen einer Sporttauglichkeitsuntersuchung auszuschöpfen. Durch die Arbeitslastindexierung können überschießende Blutdruckreaktionen als Folge einer subklinischen vaskulären Funktionseinschränkung detektiert werden. Mit unseren Untersuchungsergebnissen erleichtern wir die klinische Einschätzung eines Ausbelastungstestes bei Athleten und tragen somit zu einer besseren Risikoeinordnung bei.

6. Zusammenfassung

In dieser Arbeit wurden die Blutdruckregulation sowie die Anwendbarkeit neuer Arbeitslast-indexierter Parameter der Blutdruckantwort unter Belastung bei Leistungssportlern untersucht. Zudem wurde der Einfluss der zentralen Hämodynamik und der vaskulären Funktion auf die Blutdruckregulation sowie deren Assoziation zur Leistungsfähigkeit betrachtet. Die Messungen der zentralen Hämodynamik und der vaskulären Funktionsparameter wurden hierbei nichtinvasiv mit Hilfe eines validierten oszillometrischen Verfahrens durchgeführt.

Da es sich bei den Probanden um gesunde hochtrainierte Leistungssportler mit einem homogenen Fitnesslevel handelte, war es ferner möglich, Assoziationen zwischen dem Vitamin-D-Spiegel und der Blutdruckregulation unabhängig vom relevanten Einflussfaktor der körperlichen Fitness zu untersuchen. Wir konnten dabei nachweisen, dass es auch bei Leistungssportlern eine hohe Prävalenz (44,3 %) eines 25-OH-Vitamin-D-Mangels gibt. Ferner unterstützen unsere Ergebnisse die Theorie, dass die untere Schwelle von 30 ng/ml auch in dieser Kohorte nicht unterschritten werden sollte, um die Skelettgesundheit zu gewährleisten *(Publikation 1)*. In unseren Untersuchungen zum Einfluss von Vitamin D auf den zentralen Blutdruck waren höhere zentrale Blutdruckwerte in der Gruppe der Athleten mit insuffizienten (< 30 ng/ml) im Vergleich zu den Athleten mit suffizienten (> 30 ng/ml) 25-OH-Vitamin-D-Spiegeln zu erkennen. Dabei lagen die zentralen Blutdruckwerte der Leistungssportler mit insuffizienten Vitamin-D-Werten im Bereich der altersgleichen Normalbevölkerung, wohingegen ein suffizienter Vitamin-D-Spiegel bei Leistungssportlern mit einem niedrigeren zentralen Blutdruck assoziiert war *(Publikation 2)*. Dies spiegelt den Einfluss von Vitamin D auf die Blutdruckregulation wider, der über die Regulation des Tonus der Widerstandsgefäße bewirkt wird. Eine hohe körperliche Leistungsfähigkeit scheint diese Effekte abmildern zu können.

Diese Kompensationsmechanismen wirken auch unter körperlicher Anstrengung, sodass auch bei Vitamin-D-Mangel keine überschießende Blutdruckreaktion bei Leistungssportlern festgestellt werden konnte. Allerdings bestätigt sich auch in dieser Untersuchung, dass ein 25-OH-Vitamin-D-Mangel mit einer signifikant schlechteren Leistungsfähigkeit bei Athleten assoziiert ist. Durch die leistungsindexierte Betrachtungsweise der Blutdruckregulation unter Belastung konnte eine differenzierte Analyse dieser Assoziation vorgenommen werden *(Publikation 3)*.

Die vaskuläre Funktion unter Belastung spielt daher für die Leistungsfähigkeit eine wichtige Rolle und ist eng mit der Blutdruckregulation unter Belastung verbunden. Dass die physikalischen Parameter des globalen Gefäßwiderstandes (Resistance Index) in Ruhe bereits als unabhängige Prädiktoren der Leistungsfähigkeit bei Athleten fungieren, wiesen wir in einer Pilotstudie nach *(Publikation 4)*. Dabei waren die maximale Sauerstoffaufnahme (VO2 max.) und der Widerstandsindex die einzigen Parameter, welche die Leistungsfähigkeit bei einem standardisierten Ausbelastungstest bei männlichen Leistungssportlern vorhersagen konnten. Dies konnten wir in der Kontrollgruppe altersgleicher Männer nicht nachweisen. Diese Ergebnisse lassen vermuten, dass die Unterschiede der vaskulären Funktion zwischen Athleten und Kontrollgruppe insbesondere unter Belastungsbedingungen apparent werden und zu einer unterschiedlichen Blutdruckregulation und Leistungsfähigkeit führen.

Diesem Umstand trägt die neu für die Normalbevölkerung etablierte Arbeitslast-indexierte Charakterisierung der Blutdruckantwort in Form des SBP/MET-slope Rechnung. Wir untersuchten erstmals diesen Marker in einer größeren Kohorte von männlichen Leistungssportlern (n = 142) und konnten aufzeigen, dass er auch in dieser Population dazu geeignet ist, eine Charakterisierung der Blutdruckantwort unter Belastung vorzunehmen. Zudem wiesen wir nach, dass der bisher als normal vorgeschlagene SBP/MET-slope von 10 mmHg/MET[13] keineswegs eine normale Blutdruckantwort bei Leistungssportlern widerspiegelt, sondern allenfalls als oberes Limit angesehen werden kann. Ferner konnten wir erstmalig bei Leistungssportlern demonstrieren, dass ein steigender SBP/MET-slope mit einem höheren maximalen systolischem Blutdruck, einem höheren maximalen Pulsdruck und einem höheren ΔSBP, allerdings mit einer niedrigeren absoluten und relativen Leistungsfähigkeit, assoziiert ist *(Publikation 5)*. Diese Resultate unterstreichen den Zusammenhang zwischen vaskulärer Funktion, Blutdruckregulation und Leistungsfähigkeit bei Leistungssportlern und bestätigen unsere vorhergehenden Untersuchungen.
In einer weiteren Studie konnten wir festhalten, dass das Konzept der Arbeitslast-indexierten Beurteilung der Blutdruckantwort sowohl für Nichtsportler als auch für Sportler zur Beurteilung der Blutdruckregulation unter Belastung geeignet ist *(Publikation 6)*. Zudem konnten wir hierbei für die neu eingeführten Parameter SBP/W-slope und peak SBP/W-ratio erste Normwerte und obere Maximalwerte definieren und zugleich nachweisen, dass männliche Athleten andere Referenzwerte für die peak SBP/W-ratio im Vergleich zu Nichtsportlern benötigen. Dieser Unterschied manifestierte sich auch im Vergleich weiblicher Athleten mit der weiblichen Referenzkohorte *(Publikation 7)*. Aufgrund der von uns erstmals

ermittelten stärkeren Abweichungen zu den alters- und geschlechtsspezifischen Referenzwerten müssen für die peak SBP/W-ratio bei Athletinnen eigene Referenzwerte etabliert werden. Zwischen männlichen und weiblichen Athleten wurden zudem geschlechtsspezifische Unterschiede der neuen Parameter SBP/W-slope und peak SBP/W-ratio aufgezeigt. So wiesen weibliche Athleten im Vergleich zu männlichen Athleten einen steileren Blutdruckanstieg auf. Zudem waren deutliche Unterschiede des SBP/W-slope zwischen Sportlerinnen und der weiblichen Referenzpopulation zu erkennen, was darauf schließen lässt, dass dieser Marker bei Frauen zudem stärker von der körperlichen Fitness beeinflusst wird als bei Männern, bei denen dieser Unterschied nicht nachweisbar war. Somit sollten für weibliche Athleten eigene Referenzwerte definiert werden. Im Gegensatz dazu haben wir den SBP/MET-slope als geschlechtsunabhängigen Parameter für die Arbeitslast-indexierte Blutdruckantwort identifiziert. Da er zudem vergleichbar mit den publizierten Referenzwerten der Normalbevölkerung war, kann er zur Beurteilung der Blutdruckantwort bei einer Sporttauglichkeitsuntersuchung bei Männern und Frauen verwendet werden.

Trotz der in Ruhe bestehenden Unterschiede der vaskulären Funktionsparameter konnten diese allerdings in beiden Studien *(Publikationen 6 und 7)* die individuelle Blutdruckantwort nicht vorhersagen. Dieses Ergebnis war geschlechtsunabhängig und zudem auch bei den Kontrollpersonen nachweisbar. Hier wird die Bedeutung der vaskulären Funktion während der Belastung deutlich, die sich nicht mit Hilfe des genutzten validierten oszillometrischen Verfahrens ermitteln lässt. In Zukunft sollten weitere Anstrengungen zur validen nichtinvasiven Untersuchung der vaskulären Funktion während der Belastung unternommen werden.

Zusammenfassend konnten wir mit unseren Studien einen wertvollen Beitrag zur besseren klinischen Beurteilung der Blutdruckregulation bei Athleten leisten. Dies erleichtert die klinische Einschätzung eines Belastungstestes im Rahmen einer Sporttauglichkeitsuntersuchung. Zudem haben wir den Zusammenhang zwischen der vaskulären Funktion, Blutdruckregulation und Leistungsfähigkeit bei Athleten nachgewiesen.

7. Summary

The focus of this work was blood pressure regulation and the applicability of new workload-indexed markers of the blood pressure response to exercise in elite athletes. In addition, the influence of central haemodynamics and vascular function on blood pressure regulation and their association with performance was investigated. Measurements of central haemodynamics and vascular functional parameters were carried out non-invasively at rest using a validated oscillometric device.

Since the study participants were healthy, highly trained elite athletes with a homogeneous fitness level, it was also possible to investigate associations between the vitamin D level and blood pressure regulation independent of the level of physical fitness as a potentially confounding factor. We were able to prove that there is a high prevalence (44.3%) of 25-OH vitamin D insufficiency in elite handball athletes. Furthermore, our results support the hypothesis that 25-OH vitamin D levels should not be lower than 30 ng/mL in order to ensure skeletal health *(Publication 1)*. In our studies on the influence of vitamin D on central blood pressure, higher central blood pressure values were found in the group of athletes with insufficient (<30 ng/mL) vitamin D levels than in those with sufficient (>30 ng/mL) concentrations. The central blood pressure values of elite athletes with insufficient vitamin D values were in the range of the age-matched normal population, whereas sufficient vitamin D levels in elite athletes were associated with a lower central blood pressure *(Publication 2)*. This emphasizes the impact of vitamin D on blood pressure regulation, which is mediated by effects on the tonus of resistance vessels. A high fitness level seems to mitigate these effects.

These compensatory mechanisms also operate under exercise conditions. Even in individuals with vitamin D insufficiency, no exaggerated blood pressure response was detected in elite athletes. However, this study also confirms that a 25-OH vitamin D insufficiency is associated with significantly poorer performance in athletes. The novel approach of analysing blood pressure response to exercise with a workload-indexed method enabled a differentiated analysis of the association of vitamin D with blood pressure regulation and performance in elite athletes *(Publication 3)*.

Vascular function during exercise plays an important role in performance and is closely related to the exercise-induced blood pressure response. We demonstrated in a pilot study that the resistance index measured at rest, as a physical parameter of global vascular resistance, was an independent predictor of maximum power output in elite athletes *(Publication 4)*. The

maximum oxygen uptake (VO2 max) and the resistance index were the only parameters that were able to predict the maximum power output in male elite athletes, whereas this was not the case in the sex- and age-matched control group. These results suggest that the differences in vascular function between athletes and controls become apparent under exercise conditions and lead to a different blood pressure regulation and performance.

The newly established workload-indexed characterization of the blood pressure response to exercise using the SBP/MET slope takes this into account. We examined this marker for the first time in a larger cohort of male elite athletes (n= 142) and were able to show that it can be used in such a population to characterize the blood pressure response to exercise. In addition, we demonstrated that a SBP/MET slope of 10 mmHg/MET, which was previously suggested to be normal, does not represent a normal blood pressure response in elite athletes. Instead, it should be regarded as an upper limit. Furthermore, we were able to demonstrate for the first time that in male elite athletes an increasing SBP/MET slope is associated with a higher maximum systolic blood pressure, a higher maximum pulse pressure, and a higher ΔSBP, albeit with a lower absolute and relative performance *(Publication 5)*. These results underline the connection between vascular function, blood pressure regulation, and performance in male elite athletes and confirm our previous studies.

In another study, we were able to establish that the workload-indexed assessment of the blood pressure response to exercise is suitable for both male athletes and male non-athletes *(Publication 6)*. In addition, for the first time, we were able to define normal values and upper maximum values for the newly introduced markers SBP/W slope and peak SBP/W ratio in athletes, and we demonstrated that reference values of the peak SBP/W ratio differed between male elite athletes and male non-athletes. This difference was also evident in comparing female elite athletes with a female reference cohort *(Publication 7)*.

Due to the greater deviations from the age- and sex-specific reference values that we determined for the first time, separate reference values must be established for the peak SBP/W ratio in female athletes. In addition, we observed sex-specific differences in the new markers SBP/W slope and peak SBP/W ratio between male and female athletes. Female athletes showed a steeper increase in blood pressure during exercise than their male counterparts. In addition, we detected differences in the SBP/W slope between female athletes and the female reference population, which suggests that this marker is more influenced by physical fitness in women than in men, for whom this difference was not present. Separate reference values should therefore be defined for female athletes. In contrast, we identified the

SBP/MET slope as a sex-independent marker for the workload-indexed blood pressure response to exercise. Since it was also comparable to the published reference values for the normal population, it can be used to assess the blood pressure response in a clinical exercise test for both men and women.

Despite the differences in vascular functional parameters that exist at rest, two studies *(Publications 6 and 7)* showed that these are not able to predict the individual workload-indexed blood pressure response to exercise in athletes and non-athletes. These results highlight the impact of the dynamic vascular functional changes during exercise for these markers. Unfortunately, vascular functional parameters cannot be determined under exercise conditions using oscillometric devices, due to the measurement technique. In the future, further efforts should be directed toward the development of a valid, non-invasive examination of vascular function during exercise.

In conclusion, we were able to make a valuable contribution to improving the clinical assessment of blood pressure regulation in athletes. This facilitates the assessment of a clinical exercise test, which is an important part of a pre-participation examination of athletes. We also demonstrated the relationship between vascular function, blood pressure regulation, and performance in athletes.

8. Referenzen

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9. Schriftenverzeichnis des Verfassers

Erstautorenschaften/Letztautorenschaften

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10. Abbildungsverzeichnis

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CLINICAL FEATURES
ORIGINAL RESEARCH

High prevalence of vitamin D insufficiency in professional handball athletes

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ABSTRACT

Objectives: Vitamin D affects multiple body functions through the regulation of gene expression. In sports medicine, its influence on musculoskeletal health and performance is of particular interest. Vitamin D insufficiency might decrease athletic performance and increase the risk of musculoskeletal injuries. Several studies have demonstrated vitamin D deficiency in professional athletes; however, the prevalence of vitamin D insufficiency in professional handball players is yet unknown.

Methods: The study was planned as a prospective, non-interventional study. We examined 70 male elite handball athletes (first league) in a pre-competition medical assessment in July. Age, height, weight, body mass index, 25-OH vitamin D, calcium, and parathyroid hormone were evaluated, and a sun exposure score was calculated. Players were then divided into two groups of vitamin D levels: insufficient (<30 ng/mL) and sufficient (≥30 ng/mL).

Results: The mean 25-OH vitamin D level of the 70 players was 33.5 ± 10.9 ng/mL (median 32.2, IQR 26.5–38.9 ng/mL). Thirty-nine (55.7%) had sufficient and 31 (44.3%) insufficient levels. Athletes with sufficient vitamin D levels had significantly lower parathyroid hormone levels than athletes with insufficiency (24.9 ± 12.1 vs. 33.5 ± 15.1 ng/mL, p = 0.02). All other parameters evaluated demonstrated no significant difference between the two groups.

Conclusion: Vitamin D insufficiency is a common finding in professional handball athletes even in summer, which might negatively affect physical performance. Furthermore, it might lead to an increased risk of musculoskeletal injuries and infections. This should be evaluated in further studies.

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Introduction

Vitamin D is a fat-soluble hormone that is extremely important for bone health and immune function [1]. Recently, other relevant effects of vitamin D have been suggested, since vitamin D receptors have been identified in numerous human tissues [1,2]. Research on these extra-skeletal effects is currently increasing, and unexpected associations of low vitamin D levels with impaired health or several diseases have been reported [2,3].

Vitamin D plays a unique role compared with that of other vitamins and in reality is considered to be a hormone [1]. The human supply is mainly maintained through the production of vitamin D_3 in the skin through the influence of ultraviolet B radiation from natural sunlight [4]. In the liver, vitamin D_3 is converted into 25-hydroxyvitamin D_3 (25-OH vitamin D), which is the major circulating metabolite. Finally, the active form 1,25-dihydroxyvitamin D_3 (1,25-OH vitamin D) is produced via another hydroxylation reaction in the kidney [1]. The assessment of 25-OH vitamin D is currently seen to be the best reflection of vitamin D status [2,5–7].

Dietary vitamin D intake through natural food sources often cannot compensate for insufficient sun exposure due to low vitamin D amounts in typical Western nutrition [8]. Even an increased intake of fatty fish, which is seen to provide one of the highest amounts of vitamin D in nutrition, is not able to increase 25-OH vitamin D levels substantially [9]. Hence, the fortification of food with vitamin D to increase nutritional uptake in the general population is promoted in some countries [7,8].

Another approach for the prevention and treatment of vitamin D insufficiency in the general population is the use of oral supplements [9–11]. Despite the proven effectiveness of this procedure in different populations to improve vitamin D status [10–14], concerns about the safety considering potential overdosing have been raised [7]; also the treatment adherence within the general population was questioned [7].

Exposure to natural sunlight is seen to be the most effective way to increase 25-OH vitamin D levels [1,4,6,15]. Hence, vitamin D levels are lower in winter than in summer and depend on the specific local sunshine duration [15]. Nevertheless, even in summer, due to modern lifestyles and the consistent use of sun lotion to prevent skin cancer [16], vitamin D deficiency is a common finding in Western societies [2,4,15,17]. Furthermore, dark skin color, living in northern latitudes (>35° North), poor dietary intake, higher body mass index, and lack of physical activity are risk factors that have been identified [4,15].

In sports medicine, the effect of vitamin D on athletic performance is a topic of growing interest [10,18–21]. There is

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increasing evidence that vitamin D influences athletic performance via both its musculoskeletal and cardiovascular effects [21–24]. It was shown that lower vitamin D levels are associated with lower muscle strength and an increasing risk of muscle and bone injuries [11,22]. In young male military personnel, it was shown that the risk of bone fracture was significantly associated with lower 25-OH vitamin D levels and increased parathyroid hormone levels [25]. In professional athletes, stress fractures are common injuries, leading to long sport pauses. Additionally, vitamin D deficiency causes a prolonged recovery in these athletes [20]. Oral vitamin D supplementation improved muscle function and muscle strength in athletes in prospectively randomized, placebo-controlled trials [11,14,23] and was able to decrease injury occurrence in elite ballet dancers [11].

In addition, the immunologic and pleiotropic effects of vitamin D are of increasing relevance in the medical care of professional athletes [2,20,26]. Athletes with insufficient vitamin D status are at higher risk for upper respiratory infections [14,26], which contributes to an increased risk for training and competition pauses. Supplementation of vitamin D has positive effects on antimicrobial peptides [12], which emphasizes the immunologic effects of vitamin D [2].

Despite these findings, the prevalence of vitamin D insufficiency and deficiency in elite athletes is still high, comparable to that of non-athletes [21,27–29] with the same associated risk factors.

A major problem in the interpretation of published research is the fact that there are no accepted guidelines for the optimum level of vitamin D to ensure normal athletic performance [10,22,27]. Today, vitamin D assessment is mainly performed by measurement of serum 25-OH vitamin D levels [5,21,22,27,30], which contains the summation of 25-OH D_2 and 25-OH D_3 levels [5]. Recently, the measurements of many more vitamin D metabolites are possible [5]. With this, new discussions about the way to assess vitamin D status occurred and are ongoing, promoting further research efforts in this field [5]. Yet, so far, the assessment of 25-OH vitamin D levels is widely used and commonly accepted to reflect vitamin D status [5]. However, the classification of 25-OH vitamin D levels as deficient, insufficient, or normal is still controversial, with recommendations for the general population being inconsistent [19,21–23,27,30]. One study, which included histomorphometric analysis of bone biopsies, recommended a minimum threshold of 30 ng/mL of 25-OH vitamin D levels to maintain skeletal health [31]. Some authors regard levels >50 ng/mL to be necessary for optimal performance in athletes [10,19].

Team handball is an indoor sport with intense physical contact throughout the game. This leads to a significant burden for the musculoskeletal system and, consequently, high rates of musculoskeletal injuries can be found [32,33]. Additionally, it is a indoor sport with a higher risk of vitamin D deficiency [34]. Interestingly in this context is the fact that beach handball, which is played outdoors, has lower injury rates than indoor handball [35]. Unfortunately, there are no data about vitamin D status in beach handball compared to indoor handball available [35].

As described, an improved understanding of risk factors and possible health consequences of vitamin D deficiency in competitive athletes may help to maintain health, prevent injuries, and probably to provide an optimal performance level [11,12,21,27]. As data regarding vitamin D levels in elite handball players are currently lacking, and considering the previous published studies that revealed a high rate of vitamin D insufficiency and deficiency in competitive athletes of different sports [17,34,36,37], we hypothesized that there may be a high percentage of vitamin D insufficiency among handball athletes. We conducted this prospective study to evaluate vitamin D levels in elite handball athletes in summer, when peak levels should be reached [34,37].

Materials and methods

The following criteria for serum 25-OH vitamin D concentrations were chosen according to recently published studies and recommendations [6,13,30,31].

Values of <30 ng/mL were defined as insufficient and values ≥30 ng/mL were defined as sufficient 25-OH vitamin D levels.

To ensure comparisons to other studies, we additionally divided the athletes into four subgroups, according to the respective 25-OH vitamin D levels: <20 ng/mL, ≥20–30 ng/mL, ≥30–50 ng/mL and ≥50–75 ng/mL.

The study was carried out at the university hospital in Giessen, Germany, which is located near 50° N latitude. It was conducted as a prospective study during the routine pre-season medical monitoring program of the first German handball division in the second half of July 2016 and July 2017 after a six-week competition-free interval.

Study population

The participants were 70 healthy, injury-free professional handball athletes of varying nationalities playing in the first German handball division. All athletes were Caucasians with white skin and none of them was a regular sunbed user. None took vitamin D supplements or other multivitamin supplements. All individuals were subjected to a physical examination, 12-lead electrocardiogram, cardiopulmonary exercise test, and blood testing. Age, height, weight, body mass index, serum 25-OH vitamin D, calcium, and parathyroid hormone levels were evaluated. Players were then divided into groups according to vitamin D levels as described above, and statistical analyses were performed.

Blood samples were drawn from an antecubital vein in a sitting position. Blood samples for plasma analyses were collected into two 7.5 mL S-Monovette® tubes (Sarstedt AG & Co. KG, Germany), one containing lithium heparin. An additional 2.7 mL sample, with dipotassium ethylene diamine tetra-acetic acid (K2EDTA) as anticoagulant, was acquired (Sarstedt AG & Co. KG, Germany). Within 30 min of drawing automated analysis was performed in the laboratory of the university hospital Giessen. Serum 25-OH vitamin D concentrations were determined with a Liaison diagnostic system (DiaSorin, Stillwater, MN, USA) by chemiluminescent immunoassay (CLIA). The range of detection is 4–150 ng/mL with a precision of 5.0% CV and an accuracy SD of 1.2. Parathyroid hormone was analyzed using an electrochemiluminescent immunoassay (Elecsys PTH (1–84)®, Roche Diagnostics, Germany), which

measures the circulating active parathyroid hormone. The range of detection is 5.5–2300 pg/mL with a precision range of 2.5–3.4% CV. Furthermore, calcium levels, a complete blood cell count and a basic metabolic panel including electrolytes, were assessed and analyzed by a Modular Analytics E 170 module (Roche Diagnostics, Mannheim, Germany).

All participants received a clear explanation of the study and provided their written informed consent. The local ethics committee of the University of Giessen approved the study protocol. The study meets the ethical standards [38].

Sun exposure

Medical history, nutrition supplementation, and sun exposure were investigated with standardized questionnaires. The sun exposure questionnaire concerning individual daily sun exposure during the two weeks prior to the examination was validated for healthy Caucasians [39]. There were three choices for the amount of time spent outdoors each day, and the answers were scored using a point system (0 points for ≤5 min, 1 point for 5–30 min, and 2 points for ≥30 min). Four choices for clothing or skin exposure while outdoors were assigned points (1 point for face and hands only; 2 points for face, hands and arms; 3 points for face, hands and legs; and 4 points for bathing suit). A total score to estimate their mean weekly sun exposure resulting from the answers was then calculated. The sum of the daily products of time outdoors and skin exposure defined the score for one day, with a minimum score of '0' (lowest amount of time spent outdoors and lowest amount of skin exposed) and a maximum score of '8' (outdoors for more than 30 min in a bathing suit every day). All seven-day sun exposure scores were summed to give the weekly sun exposure score (min = 0, max = 56).

Statistical analysis

All data for continuous variables are expressed as means ± standard deviation (SD) and as median and interquartile range (IQR), as appropriate. Categorical variables are reported as numbers and percentages. After testing for normal distribution, values were compared with the unpaired Student's *t*-test or Mann-Whitney test, as appropriate. Fisher's exact test or a chi-square test was used for categorical variables with nominal scales. Intergroup comparisons were made using the Mann-Whitney test, ANOVA, or correlations and multiple linear regressions models. All statistical tests were performed two-tailed. The statistical significance level was set at $p < 0.05$. Statistical analysis was performed with the statistical software SPSS 20.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) for Macintosh.

Results

A total of 70 professional handball athletes were included in the study. They were experienced athletes and had participated in professional training for 10.1 ± 3.3 y (median 10.3, IQR 8.8–12.1 y) with a current mean training time of 17.1 ± 1.1 h (median 17.5, IQR 16.8–19.6 h) per week.

The anthropometric characteristics and specific training data of the handball players are displayed in detail in Table 1.

The mean 25-OH vitamin D level of the 70 athletes was 33.5 ± 10.9 ng/mL (median 32.2, IQR 26.5–38.9 ng/mL). The lowest measured value was 8.4 ng/mL, and the highest was 70.7 ng/mL. A total of 31 players (44.3%) were considered to have insufficient levels of 25-OH vitamin D (<30 ng/mL). Of these, 5 (7%) displayed levels <20 ng/mL, which constitutes a deficiency. In contrast, 39 players (55.7%) were considered to have sufficient levels >30 ng/mL, whereby only 4 (5.7%) of these had levels ≥50 ng/mL.

We used Spearman correlation coefficients to determine whether there were correlations between vitamin D levels and player demographics (Table 2). We found highly significant correlations between 25-OH vitamin D levels and height ($r = -0.281$, $p = 0.019$), weight ($r = -0.393$, $p < 0.001$), and body mass index ($r = -0.317$, $p = 0.008$) but not for age ($r = -0.056$, $p = 0.65$), history of training ($r = -0.025$, $p = 0.24$), or sun exposure ($r = 0.126$, $p = 0.335$).

After dividing the players into the groups 'insufficient' and 'sufficient' based on the 25-OH vitamin D levels, we found statistically significant differences only for the parathyroid hormone levels, which were significantly higher in the 'insufficient' group than in the group with sufficient levels (33.5 ± 15.1 vs. 24.9 ± 12.1 ng/mL, $p = 0.02$) (Table 3). There were no significant differences regarding age, height, weight, body mass index, sun exposure points, or training history.

Finally, we divided the athletes into additional groups of 25-OH vitamin D levels as described above (<20 ng/mL, ≥20–30 ng/mL, ≥30–50 ng/mL and ≥50 –75 ng/mL) and made comparisons between the different groups (Tables 4 and 5). We did not detect any statistically significant differences in various parameters between athletes with levels <20 ng/mL and those with levels ≥20–30 ng/mL. However, players with 25-OH vitamin D levels ≥50 –75 ng/mL had a significantly lower weight than athletes with levels ≥20–30 ng/mL ($p = 0.028$) and those with levels <20 ng/mL ($p = 0.003$). Additionally, they were significantly shorter ($p = 0.005$) than

Table 1. Characteristics of all 70 handball athletes.

	Mean ± SD	Median (IQR)
Age, years	26.3 ± 4.9	25 (23–30)
Height, cm	192.5 ± 6.3	193 (190–197)
Weight, kg	96.7 ± 9.2	97 (92–102)
Body mass index, kg/m^2	26 ± 1.7	26 (25–26.6)
Training time per week, h	17.1 ± 1.1	17.5 (16.8–18.6)
Professional training, y	10.1 ± 3.3	10.3 (8.8–12.1)

Values are given as means ± standard deviation (SD) and median with interquartile ranges (IQR).

Table 2. Spearman correlation coefficients for each variable.

	Correlation (r) with vitamin D level	p
Age	−0.056	0.65
Height	−0.281	0.019*
Weight	−0.393	0.0008*
Body mass index	−0.317	0.013*
Parathyroid hormone	−0.297	0.02*
Professional training	−0.025	0.242
Sun exposurepoints	0.126	0.335

*Statistically significant correlation ($p < 0.05$).

Table 3. Characteristics of athletes with insufficient and sufficient vitamin D levels.

	Insufficient (< 30 ng/mL) (n = 31)		Sufficient (≥ 30 ng/mL) (n = 39)		p value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Age, years	27.3 ± 5,4	26.5 (23.3–31)	25.4 ± 4.2	25 (22.5–27.5)	0.14
Height,cm	194 ± 5	195 (190–198)	191 ± 6	192 (189–196)	0.13
Weight, kg	98.9 ± 6.9	98 (96.3–103.8)	95 ± 9.4	95 (89.5–99.5)	0.09
BMI, kg/m^2	26.3 ± 1.29	26.4 (25.8–27.1)	25.8 ± 1.8	25.5 (25–26.3)	0.33
PTH, ng/mL	33.5 ± 15.1	29.3 (21.4–42)	24.9 ± 12.1	22.4 (17–33.1)	0.02[a]
Calcium, mmol/L	2.36 ± 0.12	2.4 (2.3–2.4)	2.32 ± 0.1	2.3 (2.2–2.4)	0.57
Vitamin D, ng/mL	23.2 ± 5.4	25.9 (20.3–26.5)	39.1 ± 8.7	37.1 (32.3–42.9)	< 0.01[a]
SEP, points	75.5 ± 20.7	76 (76–86,5)	84.8 ± 19.8	88 (70–102)	0.09

[a]Significant difference ($p < 0.05$)

Values are given as means ± standard deviation (SD) and as median with interquartile ranges (IQR). BMI = body mass index; PTH = parathyroid hormone; SEP = sun exposure points (measured over the two weeks prior to examination; maximum 112 points).

athletes with levels <20 ng/mL. Participants with 25- OH vitamin D levels ≥30 ng/mL (≥30–50 ng/mL and ≥50–75 ng/mL) had a significantly higher ($p < 0.05$) sun exposure score (83.6 ± 19 and 95.5 ± 23.2) than athletes with levels <20 ng/mL (53.2 ± 22.9). All other parameters examined showed no differences between groups.

Discussion

This is the first prospective study to evaluate 25-OH vitamin D levels in male professional handball players in Germany. We report a high prevalence of insufficiency (44%) even in summer, when peak levels are to be expected [34,37]. The 25-OH vitamin D levels we measured (33.5 ± 10.9 ng/mL) were lower than those of Mehran et al. [29], who found a mean level of 45.8 ± 13.7 ng/mL in male hockey players of the North American NHL (national hockey league), and lower than those of Morton et al. [37], who reported a mean level of 41.8 ± 8.4 ng/mL in professional soccer players. These studies both found a lower incidence of insufficiency and deficiency compared with our cohort. Similar to our investigation, these studies took place in a routine pre-season examination program after a competition-free interval. It is conceivable that their athletes, similar to ours, were on holidays in the weeks immediately prior to the examination. Therefore, to minimize confounders, we assessed a sun exposure score for the last 2 weeks before the examination took place. We found a high amount of sun exposure in our athletes, as the majority of them were on summer holidays. Hence, we expected higher levels of 25-OH vitamin D, as it is known that natural sunlight is the major source of vitamin D [4]. Unfortunately, these potential confounders were not raised in the other published studies [29,37]. Furthermore, there are no data given about nutrition or supplement use in their athletes. In our cohort, we assessed nutrition supplementation; none of the athletes examined took vitamin D supplements or multivitamins. Nutrition supplementation is widely used in professional sports and might contribute to the higher levels of 25-OH vitamin D levels they found.

In contrast, some investigators found lower levels of 25-OH vitamin D than we did. Maroon et al. examined athletes of the United States national football league (NFL) and reported a mean level of 27.4 ± 11.7 ng/mL [28]. Differences in the cohorts investigated might explain this result. A major differentiating factor is racial composition. In our cohort, we had exclusively white Caucasians, whereas the participants of Maroon et al. were predominantly African Americans (84%). Dark skin constitutes a well-known risk for vitamin D deficiency [4], and dark skinned athletes displayed significantly lower levels than white athletes [28]. Accordingly, in the subgroup of white athletes 25-OH vitamin D levels of 37.4 ± 8.6 ng/mL were cited [28], which is even higher than the mean levels in our study.

Krzywanski et al. [34] reported a mean level of 27 ± 1 ng/mL in Polish indoor elite athletes in summer. Interestingly, the 25-OH vitamin D levels varied significantly depending on the type of sport. Indoor athletes displayed significantly lower 25-OH vitamin D levels than outdoor athletes throughout the year,

Table 4. Characteristics of athletes according to the different 25-OH vitamin D levels.

	25-OH vitamin D levels							
	<20 ng/mL (n = 6)		≥20–30 ng/mL (n = 25)		≥30–50 ng/mL (n = 35)		≥50–75 ng/Ml (n = 4)	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Age, years	24.2 ± 6	22 (20–26)	28.2 ± 4.8	29 (25–31)	25.6 ± 4.3	25 (22–27.5)	26.8 ± 6.6	25 (24.8–27)
Height,cm	197 ± 1	197 (196–198)	193 ± 5	193 (190–196)	192 ± 6	193 (190–197)	**187 ± 4**	**187 (184–190)***
Weight, kg	102 ± 3.1	100 (100–105)	98.1 ± 7.5	98 (94–99)	95.7 ± 9.4	95 (90–100)	**88.3 ± 5.1**	**88 (84.3–92)*,****
BMI, kg/m^2	26.1 ± 0.78	26 (25.7–26.5)	26.3 ± 1.4	26.6 (26–27.2)	26 ± 1.9	25.6 (25–26.4)	25.1 ± 0.3	25 (24.8–25.3)
PTH, ng/mL	33.6 ± 12.1	32 (24.8–40)	33.5 ± 16	26.5 (21.4–42)	24.8 ± 11.4	24.2 (17.5–33.1)	26.3 ± 17.3	17.6 (15.9–28.2)
Calcium, mmol/L	2.36 ± 0.1	2.4 (2.3–2.4)	2.33 ± 0.1	2.35 (2.2–2.4)	2.36 ± 0.08	2.4 (2.3–2.4)	2.4 ± 0.07	2.4 (2.38–2.43)
Vitamin D, ng/mL	15.2 ± 4.2	14.6 (13.7–19.3)	25.7 ± 2.5	26.1 (25.6–26.7)	36.8 ± 4.9	36.9 (32.2–40)	59.8 ± 6.9	58.3 (55.9–62.2)
SEP, points	53.2 ± 22.9	52 (28–76)	75.5 ± 22.3	76 (76–88)	**83.6 ± 19**	**80 (70–102)***	**95.5 ± 23.2**	**107 (90.5–112)***

*Significant difference vs. levels of <20 ng/mL ($p < 0.05$); **Significant difference vs. levels of ≥20–30 ng/mL ($p < 0.05$). See Table 5 for specific p-values. **Bold text** signifies significant differences. Values are given as means ± standard deviation (SD) and as median with interquartile ranges (IQR). BMI = body mass index; PTH = parathyroid hormone; SEP = sun exposure points (measured over the 2 weeks prior to examination; maximum 112 points).

Table 5. p-values for comparison of values for each variable from Table 4 with the different groups, according to the respective 25-OH vitamin D levels.

	25-OH vitamin D levels			
	<20 vs. ≥20–30 ng/mL	<20 vs. ≥30–50 ng/mL	<20 vs. ≥50–75 ng/mL	≥20–30 vs. ≥50–75 ng/mL
Age	0.152	0.638	0.532	0.585
Height	0.091	0.060	0.005*	0.093
Weight	0.310	0.172	0.003*	0.028*
BMI	0.760	0.837	0.058	0.104
PTH	0.984	0.124	0.528	0.455
Calcium	0.51	0.94	0.57	0.18
SEP	0.077	0.003*	0.046*	0.144

*Significant difference ($p < 0.05$). BMI = body mass index; PTH = parathyroid hormone; SEP = sun exposure points (measured over the two weeks prior to examination; maximum 112 points).

even in summer [34]. The Polish study seems to be the most suitable to compare with our own results as it was conducted in Poland, which encompasses the same latitude (between 49 and 53° N) as the location of our own examination (50° N). Like our study and others [40], it raises concerns about indoor athletes being at higher risk for vitamin D deficiency. Furthermore, the findings of other researchers [31] that overall solar exposure is not sufficient to synthesize enough 25-OH vitamin D from 7-dehydrocholesterol in Germany are supported.

In our investigation, 25-OH vitamin D levels showed significant correlations with height, weight, and body mass index. Thus, like other researchers [41], we found a correlation between decreased height, increased weight, or increased body mass index with lower 25-OH vitamin D levels. However, when we compared the group with insufficient to those with sufficient 25-OH vitamin D levels, we could not find any significant differences in height, weight, body mass index and sun exposure score. In contrast to other published findings [29], we did not detect a significant age difference between athletes with insufficient and sufficient 25-OH vitamin D levels.

Parathyroid hormone levels, however, were significantly higher in athletes with insufficient 25-OH vitamin D levels than in those with sufficient levels. This finding is consistent with persisting bone turnover activity and constitutes a risk for bone mineralization defects [31]; bone demineralization and osteomalazia could have severe consequences for professional athletes.

Unfortunately, most other studies evaluating vitamin D levels in elite athletes did not determine parathyroid hormone levels [28,29,34,36]. In this context, it is important to mention that it is currently unclear what level of 25-OH vitamin D is necessary to maintain skeletal health. Currently, most researchers regard 30 ng/mL as an appropriate level [31]. It has been shown that levels above 30 ng/mL minimize the risk for bone mineralization defects [31]. As a consequence, we, like other researchers [28,29], chose to designate 25-OH vitamin D levels <30 ng/mL as being insufficient for our elite athletes. Our results support our strategy, since the players with sufficient levels had significantly lower parathyroid hormone levels than the players with insufficient levels and parathyroid hormone elevation was seen as risk factor for stress bone fractures in healthy young men [25]. However, more data should be obtained in the future to establish an accepted threshold of 25-OH vitamin D levels for professional athletes.

Our study also raises questions about the best strategies to maintain normal vitamin D levels to ensure skeletal health in professional handball athletes. Our investigation took place in the summer, and the participants had a high sun exposure level in the weeks before the evaluation of serum 25-OH vitamin D. We did not detect significant differences in the sun exposure of athletes with sufficient and insufficient vitamin D levels in the two weeks prior to the investigation. Yet, the prevalence of vitamin D insufficiency, defined as described above, was high. We used a standardized sun exposure questionnaire to assess sun exposure [39]. Though it was validated and has shown to predict 25-OH vitamin D levels in summer in Caucasian hospital workers, several limitations of this method have to be regarded. First, it reflects only the sun exposure during the last 2 weeks. Therefore the influence of the sun exposure prior to this time frame is neglected. Further, the widespread use of sunscreen is not represented, as well as other barrier factors (e.g. atmospheric pollution in the area). A recently published study found a low accuracy of the used sun exposure score questionnaire to estimate 25-OH vitamin D levels in young Brazilian men and women [42].

However, low solar exposure in Germany [31], consistent use of sun lotion [4], and the higher risk for indoor athletes [40] support the assumption that insufficient 25-OH vitamin D levels are partly caused by an insufficient exposure to natural sunlight. The implementation of training camps in southern regions in winter or the targeted use of sunbeds were suggested as a solution to increase 25-OH vitamin D levels in athletes [34], although this would be more complex, expensive and might cause complications like erythema in case of improper use.

Given the low amounts of vitamin D in the typical western nutrition, a vitamin D-enriched diet [8], as described before, seems to be ineffective to prevent vitamin D insufficiency [9]. Supplementation of vitamin D is an effective approach to maintain or reach sufficient 25-OH vitamin D levels in athletes [10,11,14,34]. Thus, a vitamin D supplementation only during winter, which has been proposed by other researchers [40], would also seem to be ineffective to prevent vitamin D insufficiency in professional handball athletes in Germany.

Hence, an individual vitamin D supplementation for athletes at risk throughout the year with repetitive assessment of 25-OH vitamin D levels might be a safe and sufficient solution to maintain skeletal health [31], to reduce musculoskeletal injuries [11] and to prevent upper respiratory infections [26]. Whether an improved vitamin D status influences physical performance or injury rates in professional handball players positively has to be examined in future studies.

Limitations

Several limitations should be considered in interpreting our results. First, we did not have a control group (recreational athletes or untrained persons) and assessed the 25-OH vitamin D levels at a single time point in summer. Hence, longitudinal data and information about 25-OH vitamin D levels in spring, fall and winter are missing. Second, we did not evaluate normal food behavior of the athletes to assess nutritional vitamin D uptake. This might have affected our results. Third, self-reported data via questionnaire to obtain information about sun exposure might not be the most accurate method to assess the real impact of natural sunlight

on the 25-OH vitamin D levels in our athletes. Especially the lack of evaluating sunscreen use has to be seen as a major limitation in this setting. Moreover, our study participants were all Caucasians with white skin, so that the results of our study cannot be transferred to other professional handball players in general.

Finally, we did not correlate the evaluated 25-OH vitamin D levels to physical performance or injury rate. Therefore, no such conclusion can be drawn from this study.

Conclusion/Summary

To the best of our knowledge, this is the first report on the high prevalence of vitamin D insufficiency among professional handball players in Germany. It demonstrates that elite handball players are at high risk of developing insufficiency and makes the case for an increased awareness in this athletic population. Furthermore, it raises concerns about athletes in other indoor sports who may be at high risk and should consider prevention strategies. More research efforts in these professional athlete populations are needed to investigate the clinical consequences of vitamin D levels. In further trials an assessment of sun exposure, nutrition supplementation, and parathyroid levels will be necessary to eliminate potential confounders shortly before the investigation. Whether low levels of 25-OH vitamin D contribute to an impaired performance in handball athletes or increase the risk of musculoskeletal injuries or infections should be evaluated in further prospective interventional studies.

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ORIGINAL ARTICLE

Elite athletes as research model: vitamin D insufficiency associates with elevated central blood pressure in professional handball athletes

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Abstract

Purpose Low vitamin D levels have been associated with elevated blood pressure in the general population. Prospective studies, however, have produced conflicting evidence about the blood pressure-lowering effects of vitamin D supplementation. Cardiorespiratory fitness may modulate the vitamin D–blood pressure association. We therefore examined this association in professional athletes, whose high training load serves as a biological control for physical fitness.

Methods 50 male professional handball players (age 26 ± 5 years) were examined. We assessed the central aortic pressure parameters using transfer function-based analysis of oscillometrically obtained peripheral arterial waveforms. Serum 25-OH vitamin D concentrations were determined by chemiluminescent immunoassay. The threshold for insufficiency was set at values of < 30 ng/mL.

Results Central blood pressure (cBP) was 98 ± 7/60 ± 10 mmHg. The aortic pulse wave velocity (PWV) was 6.3 ± 1.0 m/s. Nine athletes (18%) displayed insufficient 25-OH vitamin D levels and had a significantly ($p < 0.01$) higher cBP compared with the 41 (82%) athletes with sufficient 25-OH vitamin D levels (106 ± 5/68 ± 8 vs. 97 ± 7/58 ± 9 mmHg). Central systolic blood pressure (cSBP) in vitamin D-sufficient athletes was significantly lower in comparison to the healthy reference population (97 mmHg vs. 103 mmHg, $p < 0.001$). This significance of difference was lost in vitamin D-insufficient athletes (106 mmHg vs. 103 mmHg, $p = 0.12$).

Conclusion Significantly raised central systolic and diastolic blood pressure in vitamin D-insufficient elite athletes implicates vitamin D as a potential modifier of vascular functional health.

Keywords Vascular function · Elite athletes · Handball · Pulse pressure wave analysis · Vitamin D · Central blood pressure · Central hemodynamics

Abbreviations

Aix	Augmentation index
Aix@75	Augmentation index at heart rate of 75 beats per minute
BMI	Body mass index
cBP	Central blood pressure
cDBP	Central diastolic blood pressure
cSBP	Central systolic blood pressure
CRF	Cardiorespiratory fitness
CLIA	Chemiluminescent immunoassay
ECG	Electrocardiogram
K2EDTA	Dipotassium ethylene diamine tetra-acetic acid
min	Minute
MPO	Maximum power output
PTH	Parathyroid hormone
PWV	Aortic pulse wave velocity
RHR	Resting heart rate
SD	Standard deviation
VO_{2max}	Maximum oxygen uptake

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Introduction

Many observational studies associated vitamin D deficiency with arterial hypertension (Kunutsor et al. 2013), increased cardiovascular events, impaired vascular function (Al Mheid et al. 2011) and mortality (Wang 2016; Anderson et al. 2010). Vitamin D receptors were found on smooth muscle cells (Somjen et al. 2005), myocytes and endothelial cells (Norman 2008). Supplementation of vitamin D in asymptomatic deficient subjects leads to an improved endothelial function (Tarcin et al. 2009). Further, anti-inflammatory effects of vitamin D (Norman 2008) could be shown and a vitamin D-regulated reduction of the activity of the renin–angiotensin–aldosterone system was found (Forman et al. 2010). All of these mechanisms potentially mediate a blood pressure-regulating effect of vitamin D.

Hence, a causal link between 25-OH vitamin D concentrations and cardiovascular function has been hypothesized (Christakos et al. 2013; Anderson et al. 2010; Arora and Wang 2017). The sound physiological rationale for this association finds support in a genetic study (Vimaleswaran et al. 2014) and in a Mendelian randomization study of the association between vitamin D deficiency and all-cause mortality (Aspelund et al. 2019).

However, two meta-analyses have shown that vitamin D supplementation in deficient adults was ineffective in lowering peripheral or central blood pressure (Beveridge et al. 2015; Rodriguez et al. 2016). In contrast, a recently published randomized controlled trial revealed that high dose vitamin D supplementation, given monthly over 1 year, lowered central blood pressure parameters significantly in vitamin D-deficient adults (Sluyter et al. 2017).

This lack of corroborating evidence is unsurprising given that cardiorespiratory fitness (CRF), measured as maximal oxygen uptake, is a dominant predictor of cardiovascular health (Davidson et al. 2018; Lee et al. 2010). In the general population regular exercise, performed at moderate intensity, is a well-known therapeutic tool to prevent cardiovascular events and to lower blood pressure (Laurent et al. 2011; Lee et al. 2012; Yoshikawa et al. 2019). It constitutes a cornerstone of preventive medicine (Lee et al. 2012). In this context, it is easy to see how failure to control for 25-OH vitamin D status and for CRF may yield conflicting results about the benefits of 25-OH vitamin D supplementation on blood pressure. We therefore hypothesize that 25-OH vitamin D status acts as an effect modifier of the CRF–blood pressure association. We suggest to investigate this hypothesis in populations ideally drawn from the highest CRF strata of a given age bracket. Recruiting professional elite athletes from within a specified sports discipline presents such an opportunity. These athletes' maximal training load, designed to elicit maximal fitness and sports performance, constitutes a strategy of effectively controlling for CRF. It is therefore conceivable that studying the correlations between fitness, vitamin D and cardiovascular function in an elite athletic population may yield insights that would not be attainable in non-athletic normal populations whose typically wide range of physical activity behaviors and fitness levels are potential confounders to these correlations.

So far, only few studies addressed the association between 25-OH vitamin D concentration, central hemodynamics and vascular function in professional athletes, a population repeatedly reported to be vitamin D insufficient and deficient (Owens et al. 2015; He et al. 2016; Mehran et al. 2016; Maroon et al. 2015). Our group recently discovered a high prevalence of vitamin D insufficiency (25-OH vitamin D < 30 ng/mL) in professional handball athletes in Germany (Bauer et al. 2018). We conducted this study to evaluate the associations between vitamin D levels and central hemodynamics in elite handball athletes. Handball is a team sport that exposes athletes to a high hemodynamic stress with its many interval sprints. It was classified as a sport with a high dynamic component (> 75% VO_{2max}) and a moderate static component (10–20%) (Levine et al. 2015).

Athletes were studied during summer, when 25-OH vitamin D levels are expected to have reached their peak (Morton et al. 2012; Krzywanski et al. 2016). We focused our investigation on measures of central (aortic) blood pressure (cBP). cBP is more strongly related to vascular disease and outcome (Roman et al. 2007) than peripheral (brachial) blood pressure, and therefore has a greater prognostic value (Cheng et al. 2013; Fan et al. 2016; Herbert et al. 2014; Roman et al. 2007).

Materials and methods

The following criteria for serum 25-OH vitamin D concentrations were chosen according to recently published studies and recommendations (Holick et al. 2012, 2011; Pludowski et al. 2013; Priemel et al. 2010).

Values of < 30 ng/mL were defined as insufficient and values ≥ 30 ng/mL were defined as sufficient 25-OH vitamin D levels.

The study was carried out at the university hospital in Giessen, Germany, which is located near 50°N latitude. It was conducted as a prospective study during the routine pre-season medical monitoring program of the first German handball division in the second half of July 2016 and July 2017 after a 6-week competition-free interval.

Study population

The participants were 50 healthy, injury-free professional handball athletes of varying nationalities playing in the first German handball division. All athletes were Caucasians with white skin and none of them was a regular sunbed user. None took vitamin D supplements or other multivitamin supplements. All individuals were subjected to a physical examination, 12-lead electrocardiogram, cardiopulmonary exercise test, and blood testing. Age, height, weight, body mass index, serum 25-OH vitamin D, calcium, magnesium and parathyroid hormone levels (PTH) were evaluated. Players were then divided into groups according to vitamin D levels as described above, and statistical analyses were performed.

Blood samples were drawn from an antecubital vein in a sitting position. Blood samples for plasma analyses were collected into two 7.5-mL S-Monovette® tubes (Sarstedt AG & Co. KG, Germany), one containing lithium heparin. An additional 2.7 mL sample, with dipotassium ethylene diamine tetra-acetic acid (K2EDTA) as anticoagulant, was acquired (Sarstedt AG & Co. KG, Germany). Within 30 min of drawing, automated analysis was performed in the laboratory of the university hospital Giessen. Serum 25-OH vitamin D concentrations were determined with a Liaison diagnostic system (DiaSorin, Stillwater, MN, USA) by chemiluminescent immunoassay (CLIA). The range of detection is 4–150 ng/mL with a precision of 5.0% CV and an accuracy SD of 1.2. Parathyroid hormone was analyzed using an electrochemiluminescent immunoassay [Elecsys PTH (1–84)®, Roche Diagnostics, Germany], which measures the circulating active parathyroid hormone. The range of detection is 5.5–2300 pg/mL with a precision range of 2.5–3.4% CV. Furthermore, calcium levels, a complete blood cell count and a basic metabolic panel including electrolytes, were assessed and analyzed by a Modular Analytics E 170 module (Roche Diagnostics, Mannheim, Germany).

All participants received a clear explanation of the study and provided their written informed consent. The local ethics committee of the University of Giessen approved the study protocol. The study meets the ethical standards (Harriss et al. 2017).

Exercise testing

A progressive maximal cycling ergometer test with concurrent brachial blood pressure measurement and ECG recording was performed (Schiller AG®, Switzerland). The exercise test protocol started with a load level of 100 W after a 2-min warm-up period, which was conducted with 50 W. Loads were increased by 50 W every 2 min until exhaustion, which was defined as the participants' inability to maintain the load for 2 min. Next, the load was decreased to 25 W for 3 min of active recovery, followed by a cool-down period at rest of 2 min. The test concluded with a final ECG recording and a brachial blood pressure measurement. We assessed the maximum power output (MPO) of the athletes, maximum heart rate, heart rate at rest and after the exercise test, and systolic and diastolic brachial blood pressure at rest, during and after exercise.

Noninvasive assessment of peripheral and central blood pressure and pulse pressure waveforms

We used the noninvasive vascassist2® device (isymed GmbH, Butzbach, Germany) to acquire pulse pressure waveforms by means of oscillometry. The device uses a validated model (Schumacher et al. 2018) of the arterial tree, representing all central and peripheral arterial sections. By modulating the circuits' capacitance, resistance, inductance, and voltage, the system replicates an individual's acquired pulse pressure waves. The system is based on the premise that the parameters used to replicate the pulse pressure waves are a quantitative representation of the functional parameters that gave rise to the pulse pressure wave in the biological original. The vascassist2® system uses genetic algorithms to optimize the fidelity of the pulse pressure wave replication (Schumacher et al. 2018). Fidelity replications of 99.6% or above were included in the analysis.

The noninvasive vascular evaluation was performed before the exercise testing in all athletes. After a 15-min rest, measurements were performed in a supine position using four conventional cuffs adapted to the arm and forearm circumference of the athletes. Radial and brachial pulse pressure waves were acquired on both arms with step-by-step deflation of the cuffs. The measurements took place in a room with a comfortable temperature of 22 °C and a lack of external stress influences. Participants were advised not to move during the acquisition of pulse pressure waves. Two brachial and three radial measurements were performed to guarantee stable and valid results. The total duration of the examination was 15 min. The acquired pulse pressure waves then were analyzed with a validated electronic model of the arterial tree to assess vascular functional parameters. Brachial and radial systolic and diastolic blood pressure, central systolic and diastolic blood pressure, pulse wave velocity (PWV), augmentation index (Aix), augmentation index at a heart rate of 75 bpm (Aix@75), resistance index, and ejection duration were calculated. cBP was determined with a transfer function that was based on the peripheral arterial waveform. Calculation of Aix@75 was also based on the pulse waveform.

Comparison with reference population

We compared central blood pressure values with those published for a reference population of 20- to 29-year-old healthy adults (Herbert et al. 2014). As the authors reported the distribution as percentiles, we used the z-scores that correspond to the 10th and 90th percentiles to extract the standard deviation of the distribution. As these percentiles were located symmetrically around the mean the assumption of normality of the distribution, as a pre-requisite for the z-score transformation, is justified.

Statistical analysis

Data are presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to determine normal distribution. In case of skewed distribution of the data, all analyses were performed on normalized data. Between-group comparisons were performed using independent-samples t tests. Bivariate relations were analyzed using Pearson's product–moment correlation coefficient.

Statistical significance was set at $p < 0.05$ two-tailed for all measurements. All statistical analyses were performed using Stata Statistical Software: Release 15. (StataCorp. 2017. College Station, TX: StataCorp LLC) for Macintosh.

Results

A total of 50 professional handball athletes were included in the study. They were experienced athletes and had participated in professional training for 9.8 ± 4.5 years (median 8.5, IQR 7–13 years) with a current mean training time of 18.6 ± 3.0 h (median 19, IQR 16.7–20 h) per week (Table 1).

41 athletes (82%) displayed sufficient 25-OH vitamin D levels of ≥ 30 ng/mL and 9 athletes (18%) were found to be vitamin D insufficient (< 30 ng/mL).

There were no significant between-group differences in age and anthropometrics. As expected, the 25-OH vitamin D levels between the sufficient and insufficient groups (41.3 ± 8.7 ng/mL vs 21.1 ± 7.9 ng/mL) were significantly different at $t(48) = 6.37$, $p < 0.001$). Table 2 shows the between-group comparison for all measured parameters.

Of the hemodynamic parameters, all central and peripheral blood pressure values were significantly higher in athletes with insufficient 25-OH vitamin D levels compared to those with sufficient levels. Amplification of systolic pressure was not significantly different between groups (Table 2).

Athletes with sufficient 25-OH vitamin D levels displayed both a significant lower central diastolic (58 ± 9 vs. 68 ± 8 mmHg, $p = 0.002$) and central systolic blood pressure (97 ± 7 vs. 106 ± 5 mmHg, $p < 0.001$) compared to those athletes with insufficient levels. Further, the mean central blood pressure of the group with sufficient 25-OH vitamin D levels was significantly lower (73 ± 8 vs. 83 ± 6.5 mmHg, $p = 0.001$) (Fig. 1).

Calcium, magnesium and PTH concentrations were not significantly different between groups. Lack of power was the probable reason for the lack of between-group differences in PTH. As there exists an inverse relationship between vitamin D and PTH levels, we used Pearson product–moment correlation coefficient to examine the relationships between 25-OH vitamin D and PTH and calcium levels across the entire group. There were moderate negative correlations between 25-OH vitamin D and PTH levels, $r(48) = -0.35$, $p = 0.015$, and between PTH and Calcium, $r(48) = -0.30$, $p < 0.05$.

cSBP in our vitamin D-sufficient athletes was significantly lower than in the healthy reference population [97 mmHg vs. 103 mmHg, $t(919) = -4.36$, $p < 0.001$]. This significance of difference was lost in vitamin D-insufficient athletes with 106 mmHg vs. 103 mmHg [$t(886) = 1.17$, $p = 0.12$]. Detailed data are given in Table 3.

Systolic pressure amplification was significantly higher both in vitamin D sufficient and insufficient athletes compared to the reference population, with 26 mmHg (± 5 mmHg) and 25 mmHg (± 3 mmHg) vs. 15 mmHg (± 7 mmHg) at $t(919) = 9.94$, $p < 0.001$ and $t(886) = 4.04$, $p < 0.001$, respectively.

Also, none of our athletes exceeded the upper normative limit for maximal systolic blood pressure response of 247 mmHg that has been established for Olympic athletes during maximal exercise testing (Caselli et al. 2016).

Table 1 Characteristics of all 50 handball athletes

	Mean	SD
Age (years)	25.7	5
Height (cm)	191.2	6.4
Weight (kg)	94.8	8.9
Body mass index (kg/m^2)	25.9	1.5
History of training (years)	10.2	4.9
Training per week (h)	18.95	2.2

Discussion

To the best of our knowledge, our study is the first to investigate central blood pressure (cBP) of elite handball players in Germany and its correlation to 25-OH vitamin D status.

Our main findings are that there exists a strong correlation between vitamin D insufficiency and elevation of cBP in professional handball athletes with a significantly lower cBP in athletes with sufficient compared to those with

Table 2 Comparison of the different characteristics according to 25-OH vitamin D levels

	25-OH vitamin D levels				
	30 ng/mL		< 30 ng/mL		*p* value
	n = 41		*n* = 9		
	Mean	SD	Mean	SD	
25-OH vitamin D (ng/mL)	41.3	8.7	21.1	7.9	**< 0.001**
Age (years)	25.7	5	27.5	4.6	0.325
Weight (kg)	93.9	9.9	94.3	11.2	0.911
Height (cm)	190.1	5.6	191.9	9.2	0.689
BMI (kg/m^2)	25.7	2.13	25.5	1.3	0.800
Heart rate at rest (bpm)	55.4	9.1	55.7	6.0	0.931
Central systolic blood pressure (mmHg)	97	7.1	105.8	5.4	**< 0.001**
Central diastolic blood pressure (mmHg)	57.9	8.7	67.8	8.1	**0.002**
Central mean arterial blood pressure (mmHg)	73.2	7.8	82.9	6.5	**0.001**
Aortic pulse pressure (mmHg)	39.5	7	38	6.5	0.575
Systolic blood pressure amplification (mmHg)	25.9	5	24.8	3	0.533
Brachial systolic blood pressure (mmHg)	122.9	8.3	130.6	7.2	**0.013**
Brachial diastolic blood pressure (mmHg)	58.6	8.6	67.4	8.4	**0.008**
Mean brachial arterial blood pressure (mmHg)	74.4	8.2	83.7	6.7	**0.003**
Brachial pulse pressure (mmHg)	64.3	10.9	63.2	8.9	0.776
Pulse pressure amplification (mmHg)	24.9	5.3	25.2	3.2	0.863
Aortic pulse wave velocity (m/s)	6.3	1	6.9	0.9	0.105
Augmentation index @75 (%)	-0.2	0.1	-0.2	0.1	0.446
Maximum heart rate (bpm)	175.8	9.2	167.4	17.2	0.079
Maximum systolic brachial blood pressure (mmHg)	189	19.5	191	26.9	0.799
Maximum diastolic brachial blood pressure (mmHg)	87.3	8.7	86.7	7.4	0.842
Parathyroid hormone (pg/mL)	32.2	21	44.9	13	0.107
Calcium (mmol/L)	2.37	0.09	2.36	0.24	0.824
Magnesium (mmol/L)	0.83	0.05	0.79	0.07	0.090

Bold text signifies significant differences. Values are given as means ± standard deviation (SD)

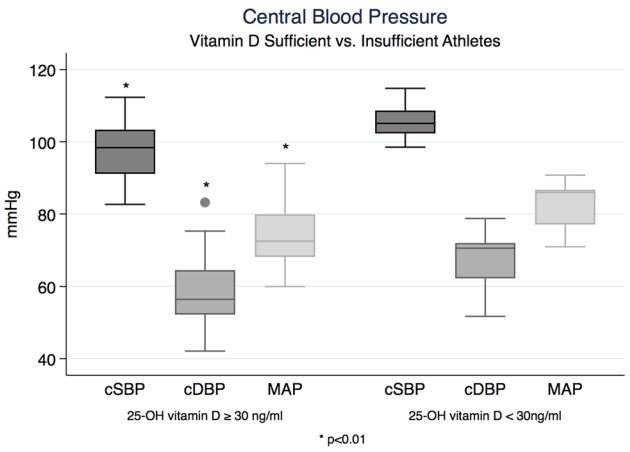

Fig. 1 Central blood pressure according to 25-OH vitamin D levels

insufficient 25-OH vitamin D levels. In addition, athletes with sufficient 25-OH vitamin D concentrations displayed a significantly lower central systolic blood pressure (cSBP) compared with age-matched non-athletic healthy persons, as reported in literature (Herbert et al. 2014). Further, we found that this hemodynamic advantage was lost in the vitamin D-insufficient athletes.

These findings strongly support the acknowledged association between vitamin D insufficiency and markers of impaired vascular function, such as arterial stiffening, endothelial dysfunction (Norman 2008; Tarcin et al. 2009) and up-regulation of the renin–angiotensin–aldosterone system (RAAS) (Forman et al. 2010).

Our focus on cBP rather than peripheral BP has been guided by three considerations. First, as described by Poiseuille's law, pressure is the product of flow and systemic resistance. Second, systemic resistance and vascular compliance are the main regulators of pressure and flow, thereby reflecting the functional integrity of the vascular system. Third, cBP is determined by the complex interaction between aortic compliance and elasticity and the resistance arteries' ability to channel blood flow in accordance with tissue needs (Stephen Hedley and Phelan 2017). Hence,

Table 3 Systolic central blood pressure and amplification of systolic blood pressure of the athletes according to 25-OH vitamin D levels in comparison with the published data of the age-matched healthy reference group (Herbert et al. 2014)

	Athletes according to 25-OH vitamin D levels					
	Reference group		≥ 30 ng/ml		< 30 ng/mL	
	Mean	SD	Mean	SD	Mean	SD
Central systolic blood pressure (mmHg)	103	8.6	**97**	**7.1**	105.8	5.4
Systolic blood pressure amplification (mmHg)	15	7	**25.9**	**5**	**24.8**	**3**

Bold text signifies significant differences compared to values of the reference group. Values are given as means ± standard deviation (SD)

central blood pressure is superior to brachial blood pressure in identifying changes of vascular functional parameters (Hodson et al. 2016) and cardiovascular risk (CVD) (Williams et al. 2006; Roman et al. 2007; Cheng et al. 2013; Fan et al. 2016; Herbert et al. 2014). A loss of distensibility in the central elastic arteries compromises their ability to buffer the ejected blood volume from the left ventricle, leading to an increase in cBP and to compromised coronary flow (Roman et al. 2007; Thijssen et al. 2016). Elevated peripheral resistance resulting from increases in vessel constriction and/or blood viscosity may amplify cBP elevations (Ashor et al. 2014). The impact of aortic stiffness on the development of cardiovascular disease has been documented in several studies (Mitchell 2009; Roman et al. 2007). An early return of the reflected pressure wave contributes to increases in cBP and arterial wall stress (Kaess et al. 2012; Green and Smith 2018), which constitutes an increased risk for cardiovascular and cerebrovascular events (Roman et al. 2007; Fan et al. 2016).

Our observation of significantly raised central systolic and diastolic pressure in vitamin D-insufficient athletes implicates vitamin D as a potential modifier of vascular functional health. As diastolic pressure is largely determined by peripheral resistance, one may speculate that vitamin D possibly affects the vascular tone of resistance vessels. Particularly in young men, cDBP, but not peripheral systolic pressure, is a predictor of cardiovascular risk (Wilkinson et al. 2001). This observation explains why brachial systolic pressure in adults younger than 50 years may be an unsuitable marker for examining the hypothesized association between vitamin D and cardiovascular risk.

Only few studies have been performed about the correlation between central hemodynamic parameters and training status in an athletic population, and none, to the best of our knowledge, has been controlled for vitamin-D status.

One study that has recently been published (Denham et al. 2016) presented evidence about significantly reduced augmentation index (Aix) in endurance-trained athletes vs. healthy untrained controls. In this mixed-gender population, the difference in cSBP between athletes and controls was not significant (106 ± 9 mmHg vs. 110 ± 9 mmHg, $p = 0.07$). The presented cSBP in the athletic population was comparable to our findings in the group of athletes with insufficient 25-OH vitamin D levels, though in our study male athletes with sufficient 25-OH vitamin D levels displayed a lower cSBP. This is consistent with the data of Denham et al. (2016), acknowledging the fact that their cohort was older than our study population. Unfortunately, lack of assessment of 25-OH vitamin D precludes controlling for vitamin-D status and limits the comparison to our results.

In a study investigating arterial stiffness in young professional rowers (mean age 24 years), a cSBP of 107 ± 11 mmHg was reported (Franzen et al. 2016) which is even higher than in our handball athletes with insufficient 25-OH vitamin D levels. This study included female athletes; cBP of healthy women should be lower than those of men (Herbert et al. 2014). Unfortunately, the results are not presented by gender. Therefore, the reported values are assumable lower than those, if only the results of the male athletes would have been presented. Interestingly, the reported PWV in this study cohort was comparable to our own results (6.6 ± 1.2 vs. 6.3 ± 1 m/s) (Franzen et al. 2016). Thus, again, vitamin D status of the professional rowers was not evaluated, which constitutes a major limitation in the comparison of the results, too.

Sotiriou et al. (2019) recently published data investigating arterial adaptations in different sports. They examined male athletes and found a lower cDBP (73 ± 12 vs. 77 ± 10.4 mmHg) and lower cSBP (99 ± 12 vs. 104 ± 14 mmHg) in high- level static sports athletes compared to high-level dynamic sports athletes (Sotiriou et al. 2019). The presented data of highly trained male athletes, performing a dynamic sport, are the most suitable for comparison with our own results. Despite the fact that their cohort was older than ours and vitamin D status was not obtained; cBP was comparable to those of our group with insufficient vitamin D levels.

Another study investigated central hemodynamics in ultra-endurance triathlon athletes (mean age 34) (Knez et al. 2008). The reported cDBP und cSBP are comparable with our results of the 25-OH vitamin-insufficient group (106 ± 8/72 ± 7 mmHg vs. 106 ± 5/68 ± 8 mmHg),

but higher than the results of our 25-OH vitamin-sufficient group (97 ± 7/58 ± 9 mmHg). Again, data about vitamin D status are missing and mixed-gender data are presented. As reported in this study, the influence of physical exercise on cBP was higher than on brachial blood pressure (Knez et al. 2008).

All results of cBP presented in these studies did not exceed the age-matched reference values for the healthy general population (Herbert et al. 2014). Hence, our findings of significantly lower cBP in a homogenous population of healthy, vitamin D-sufficient and well-trained athletes, highlights the potential blood-pressure-modifying influence of vitamin D. In general, a major limitation in comparing our results to those of the mentioned other studies is their lack of control for 25-OH vitamin D status.

Conversely, studies investigating the effects of vitamin D supplementation on central hemodynamics typically lack controlling for training and fitness status, though the blood pressure-lowering effects of exercise are well known, and regular exercise, performed at moderate intensity, is a recommended therapeutic tool in the treatment of arterial hypertension (Laurent et al. 2011; Lee et al. 2012; Yoshikawa et al. 2019). In this context, our study represents the first attempt at disentangling the interaction between central hemodynamics and 25-OH vitamin D status while effectively controlling for training status using elite athletes.

The fact that our athletes with sufficient 25-OH vitamin D levels displayed a significantly lower cBP compared to an age-matched healthy cohort motivates us to hypothesize that even the extreme exercise loads that characterize professional handball training correlate with increased cardiovascular function compared to healthy age-matched reference populations.

While exercise training typically improves markers of arterial function in a dose–response relationship (Green and Smith 2018; Rodriguez et al. 2016; Sluyter et al. 2017; Scragg et al. 2017), one study has found significant elevations of cBP and PWV in endurance-trained marathon runners (Vlachopoulos et al. 2010). Others have reported an unexpectedly high incidence of atherosclerosis in these endurance athletes (Merghani et al. 2017). These findings have stimulated the discussion of sports-related cardiovascular damage in professional athletes, resulting in the "extreme exercise hypothesis", which suggests an upper threshold for exercise. Exceeding this threshold may promote cardiac injury and atherosclerosis (La Gerche and Heidbuchel 2014; La Gerche et al. 2012; Eijsvogels et al. 2018). Our cohort of elite handball athletes had a training amount of nearly 19 h per week, though cBP and PWV in the vitamin D-sufficient athletes were lower than those of age-matched controls, suggesting a better cardiovascular function compared to them. Yet, this advantage was lost in the group with insufficient 25-OH vitamin D levels, as they displayed similar and not statistically different cBP compared to the age-matched reference group. This finding raises the question whether vitamin D may act as a modifier of the association between physical activity and its subsequent cardiovascular benefits.

Contrary to central and peripheral blood pressure, we observed no between-group difference in pulse pressure amplification. There exists a strong inverse linear relationship between pulse pressure amplification and age (Wilkinson et al. 2001). Decreasing pulse pressure amplification therefore is a strong correlate of the age-dependent decline in vascular function, specifically impaired vessel compliance (inverse of vessel stiffness) and increased systemic resistance. Our athletes showed a mean pulse pressure amplification ratio of 1.64 ± 0.1, which corresponds to 64% pulse pressure amplification from central to brachial. This can be considered normal compared to age-matched healthy persons (Wilkinson et al. 2001) and similar results were found in ultra-endurance triathlon athletes with 1.5 ± 0.2 (Knez et al. 2008). We found no significant differences in pulse pressure amplification between vitamin D sufficient and insufficient athletes, despite the fact of significantly different brachial and cBP.

These findings of higher brachial and cBP in vitamin D-insufficient athletes without a difference in pulse pressure amplification might be explainable with vitamin D insufficiency creating a functional environment that necessitates a higher pressure (at rest) for optimal blood supply, without impairment of the vasculature's age-adequate functional abilities. For example, an increase of vascular tone in resistance vessels at rest may be offset by maintained vessel compliance, ensuring the ability of maximal exercise capacity when needed. This would explain why vitamin D supplementation has largely failed as an ergogenic aid. Despite increasing research efforts regarding the effects of vitamin D on vascular cell function, cardiomyocytes and arterial function in different regions of the human vasculature, the exact physiological impact of vitamin D is still unclear (Wang 2016; Tarcin et al. 2009; Somjen et al. 2005; Forman et al. 2010).

Hence, it might be possible that vitamin D and physical activity differentially affect cardiovascular functional health. The exercise load to which our athletes have been routinely exposed may compensate for the deleterious effects of vitamin D insufficiency on the specific markers of vascular function that determine pulse pressure amplification, arterial stiffness and cBP. This potential compensatory effect of exercise highlights its modifying role in the association of vitamin D with cardiovascular risk in the general population.

Limitations

Our study has noteworthy limitations. The number of participants limited its power to uncover potential correlations between 25-OH vitamin D status and markers of cardiac and vascular function other than blood pressure. The focus on elite handball players may limit the results' extrapolation to other sport disciplines. However, as a team sport that exposes athletes to hemodynamic stresses of frequent interval sprints, it represents similar sports with a high dynamic component (> 75% VO_{2max}) and a moderate static component (10–20%) (Levine et al. 2015).

A further limitation is our exclusive focus on male athletes, which precludes the extrapolation of our results to female athletes. We are currently addressing all three issues through extension of our research to include larger numbers of professional male and female athletes from various sports disciplines.

Conclusion

In conclusion, we have shown for the first time that elite handball athletes with insufficient 25-OH vitamin D levels display a significantly higher cBP compared to those with sufficient 25-OH vitamin D levels, implicating vitamin D as a potential modifier of cBP. Further, we demonstrated that cBP was significantly lower in elite athletes with sufficient 25-OH vitamin D levels compared to the age-matched reference group, whereas this advantage was lost in athletes with insufficient 25-OH vitamin D levels.

We suggest that highly trained athletic populations present a unique opportunity to address the modifying effect of CRF on the association of 25-OH vitamin D with cBP and cardiovascular risk markers. Such investigations may offer an effective means to generate hypotheses in a cost- and time-efficient way that may subsequently be tested for their applicability in preventing and treating cardiovascular risk in the general population.

While our group of elite athletes was too small to generate authoritative insights into the complex relationship between fitness, exercise, vitamin D and cardiovascular functions, our results serve to stimulate future investigations into the correlation of vitamin D with parameters of vascular function and their response to vitamin D supplementation in vitamin D insufficient athletes.

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Author contributions PB, AM, CH, OD, HN contributed to the conception and design of the study. PB, AM, LK, SH, ST contributed to the acquisition, analysis, or interpretation of data for the work. PB and AM drafted the manuscript. PB, AM, LK, SH, ST, OD, HN critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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ORIGINAL ARTICLE

Association of 25-hydroxy vitamin D level with the blood pressure response to a maximum exercise test among professional indoor athletes

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Abstract

Purpose Low vitamin D levels have been associated with elevated blood pressure (BP) in the general population. However, whether there is an association of vitamin D insufficiency with BP changes during maximum exercise in athletes is currently unclear.

Methods A total of 120 male professional indoor athletes (age 26 ± 5 years) were examined. BP was measured at rest and during a graded cycling test. We assessed the BP response (BPR) during maximum exercise and the respective load. BP and BPR (peak-baseline BP) were analysed with respect to 25-OH vitamin D levels, with levels < 30 ng/mL defining vitamin D insufficiency.

Results 35 athletes were classified as being vitamin D insufficient. BP was not different between sufficient and insufficient vitamin D groups (122 ± 10/75 ± 7 vs. 120 ± 12/77 ± 9 mmHg). At maximum exercise, however, systolic BP (198 ± 17 vs. 189 ± 19, $p = 0.026$) and the pulse pressure (118 ± 18 vs. 109 ± 21 mmHg, $p = 0.021$) were higher in the sufficient group; the BPR was not different between groups (76 ± 20/5 ± 6 vs. 69 ± 22/3 ± 6 mmHg, $p = 0.103$). Athletes with sufficient levels had a higher maximum power output (3.99 ± 0.82 vs. 3.58 ± 0.78 W/kg, $p = 0.015$) and achieved higher workloads (367 ± 78 vs. 333 ± 80 W, $p = 0.003$). The workload-adjusted BPR (maximum systolic BP/MPO) was not different between athletes with sufficient and insufficient vitamin D levels (51 ± 10 vs. 56 ± 14 mmHg × kg/W, $p = 0.079$).

Conclusion Athletes with sufficient vitamin D achieved a higher maximum systolic BP and a higher maximum power output. The workload-adjusted BPR was not different between groups, which suggests that this finding reflects a better performance of athletes with sufficient vitamin D.

Keywords Exercise test · Professional athletes · Indoor sports · Performance · Vitamin D · Blood pressure response · Hypertension

Abbreviations

BP	Blood pressure
BPR	Blood pressure response
cBP	Central blood pressure
ECG	Electrocardiogram
K2EDTA	Dipotassium ethylenediamine tetra-acetic acid
MPO	Maximum power output
SD	Standard deviation
VO2max	Maximum oxygen uptake

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Introduction

Insufficiency and deficiency of 25-OH vitamin D have been shown to be associated with arterial hypertension (Kunutsor et al. 2013; Wang 2016), increased cardiovascular events, impaired vascular function (Al Mheid et al. 2011), and even cardiovascular mortality (Wang 2016; Anderson et al. 2010; Vimaleswaran et al. 2014). The fact that vitamin D receptors

are found throughout the cardiovascular system, in particular in smooth muscle cells (Somjen et al. 2005), myocytes, and endothelial cells (Norman 2008), suggests an impact of vitamin D on cardiovascular function. Further, it was found that supplementation of vitamin D in asymptomatic deficient subjects leads to improved endothelial function and evokes a relaxation of smooth muscle cells (Tarcin et al. 2009). Vitamin D regulated reduction of the activity of the renin–angiotensin–aldosterone system also bespeaks a crucial role of vitamin D in the cardiovascular system (Forman et al. 2010). Taken together, all of this evidence points to mechanisms that potentially mediate a blood pressure-regulating effect of vitamin D.

Healthy individuals with normal blood pressure (BP) at rest but an exaggerated BP response (BPR) during exercise are at higher risk of developing arterial hypertension (Lewis et al. 2008; Holmqvist et al. 2012). In addition, a recent meta-analysis revealed that exercise-induced systolic BP ≥ 196 mmHg predicted cardiovascular events with a sensitivity of 62% and a specificity of 75% (Percuku et al. 2019). The clinical impact of BP response during exercise, however, remains a controversial issue (Kim and Ha 2016; Schultz et al. 2015), and upper reference values for the general population are not well established (Schultz et al. 2013; Gupta et al. 2007; Weiss et al. 2010; Currie et al. 2018). The European Society of Cardiology states in its latest guideline that there is currently no consensus on normal BPR during exercise (Williams et al. 2018). In previous guidelines, a systolic peak BP of 210 mmHg for men and 190 mmHg for women were proposed as diagnostic thresholds for the general population (Mancia et al. 2013). Recommendations for athletes are absent in both guidelines, yet recently published studies proposed different thresholds for defining an exaggerated BPR to exercise (Caselli et al. 2019; Pressler et al. 2018). A higher exercise-induced BP response in athletes was explained as representing a superior exercise performance compared with that of the general population (Caselli et al. 2016). Thus far, there is no consensus about "normal" and "exaggerated" BPR in athletes. In addition, the clinical relevance of "exaggerated" exercise-induced BP in athletes is currently unclear, although a higher risk for development of arterial hypertension in these athletes was suggested (Caselli et al. 2019). In competitive triathletes, an exaggerated BPR to exercise testing was associated with a higher prevalence of myocardial fibrosis (Tahir et al. 2018), raising concerns about potential arrhythmic consequences, including sudden cardiac death (Zorzi et al. 2016).

To date, only a few studies have addressed the BPR to maximum exercise in elite athletes (Pressler et al. 2018; Caselli et al. 2019), and none of these studies reported 25-OH vitamin D status. Vitamin D insufficiency and deficiency is commonly found in athletic populations (Owens et al. 2015; He et al. 2016; Mehran et al. 2016; Maroon et al. 2015). Our group recently discovered a high prevalence of vitamin D insufficiency (25-OH vitamin D < 30 ng/mL) in professional handball athletes in Germany (Bauer et al. 2018). Further, we recently demonstrated that vitamin D-insufficient elite handball athletes displayed a significantly higher peripheral and central BP compared with the values in athletes with sufficient vitamin D levels (Bauer et al. 2019).

Given the acknowledged physiological influences of vitamin D on endothelial and smooth muscle cells (Somjen et al. 2005), the haemodynamic effects of vitamin D insufficiency might be amplified during exercise. As regular exercise, performed at moderate intensity, is a well-known therapeutic tool for lowering BP (Williams et al. 2018), it is obvious that controlling for both vitamin D and cardiorespiratory fitness status is necessary to gain reliable insights about the impact of vitamin D on BP at rest and the BPR to exercise.

Therefore, this study was undertaken to evaluate the association between 25-OH vitamin D levels, brachial BP at rest, and the BPR to a maximum exercise test in elite indoor athletes. Both handball and ice hockey, with their many interval sprints, are team sports that expose athletes to a high haemodynamic stress. Both were classified as a sport with a high dynamic component (> 75% VO2max) and a moderate static component (10–20%) (Levine et al. 2015). In addition, both are indoor sports with a higher risk of vitamin D insufficiency compared to outdoor sports (Krzywanski et al. 2016).

Materials and methods

The study was carried out at the university hospital in Giessen, Germany, which is located near 50° N latitude. It was conducted as a cross-sectional study of professional athletes during the routine pre-season medical monitoring program of the first German handball division and the second German ice hockey division. Data were collected in the second half of July in the years 2015–2018. Athletes were studied during the summer, when 25-OH vitamin D levels are expected to have reached their peak (Morton et al. 2012; Krzywanski et al. 2016).

The following criteria for serum 25-OH vitamin D concentrations were chosen according to recently published studies and recommendations (Holick et al. 2011, 2012; Pludowski et al. 2013; Priemel et al. 2010): values < 30 ng/mL were defined as insufficient and values ≥ 30 ng/mL were defined as sufficient 25-OH vitamin D levels.

The examination took place at noon between 12:00 and 14:00 o'clock and was scheduled in the 1st week of the new season after a 6-week competition-free interval. The last time athletes had trained was 36 h prior to the study beginning; the last meal was breakfast approximately 3 h before the investigation. There was no restriction of caffeine

intake provided. Thus, alcohol consumption was prohibited the two days prior to the study beginning. The day before the examination was filled with commercial dates without physical effort.

Study population

The participants were 120 healthy, injury-free professional handball and ice hockey athletes of varying nationalities. All athletes included were Caucasians with white skin and none of them was a regular sunbed user. None took vitamin D supplements or other multivitamin supplements. All individuals were subjected to a physical examination, 12-lead electrocardiogram (ECG), cardiopulmonary exercise test, and blood testing. Age, height, weight, body mass index, serum 25-OH vitamin D, calcium, magnesium and parathyroid hormone levels were determined. Body surface area was calculated using the formula of DuBois (Du Bois and Du Bois 1989). Maximum workload, maximum power output, heart rate at rest, brachial BP at rest, maximum heart rate, and maximum BP were assessed. Players then were divided into groups according to vitamin D levels as described above, and statistical analyses were performed.

Laboratory testing

Blood samples were drawn from an antecubital vein in a sitting position. Blood samples for plasma analyses were collected into two 7.5 mL S-Monovette® tubes (Sarstedt AG & Co. KG, Germany), one containing lithium heparin. An additional 2.7 mL sample, with dipotassium ethylenediamine tetra-acetic acid (K2EDTA) as anticoagulant, was acquired (Sarstedt AG & Co. KG, Germany). Automated analysis was carried out within 30 min of blood draw. Serum 25-OH vitamin D concentrations were determined with a Liaison diagnostic system (DiaSorin, Stillwater, MN, USA) by chemiluminescent immunoassay. The range of detection is 4–150 ng/mL with a precision of 5.0% CV and an accuracy SD of 1.2. Parathyroid hormone was analysed using an electrochemiluminescent immunoassay (Elecsys PTH (1–84)®, Roche Diagnostics, Germany), which measures the circulating active parathyroid hormone. The range of detection is 5.5–2300 pg/mL with a precision range of 2.5–3.4% CV. Furthermore, calcium levels, a complete blood cell count, and a basic metabolic panel including electrolytes were assessed and analysed by a Modular Analytics E 170 module (Roche Diagnostics, Mannheim, Germany).

All participants received a clear explanation of the study and provided their written informed consent. The local ethics committee of the University of Giessen approved the study protocol. The study meets current ethical standards (Harriss et al. 2017).

Blood pressure measurements at rest before the exercise testing

Resting brachial BP was measured before the exercise testing using a validated automatic device based on a standard sphygmomanometer technique (Boso clinicus, Bosch + Sohn GmbH & Co. KG, Germany). The cuff used for measurement was adjusted to the individual's arm circumference. Measurements were performed by a trained research associate on both arms in a sitting position after a resting period of 5 min and repeated after 2 min. The average BP for each arm was calculated and the highest value was used for statistical analyses. Athletes with a resting BP > 140 mmHg systolic or > 90 mmHg diastolic were excluded from the study.

Exercise testing and assessment of maximum blood pressure

Athletes underwent a progressive maximal cycling ergometer test with concurrent automatic brachial BP measurement and ECG recording (Schiller AG®, Switzerland). The exercise test protocol started with a load level of 100 W after a 2-min warm-up period that was conducted with 50 W. Loads were increased by 50 W every 2 min until exhaustion, which was defined as the participant's inability to maintain the load for 2 min. Next, the load was decreased to 25 W for 3 min of active recovery, followed by a 2-min cool-down period at rest. The test concluded with a final ECG recording and a brachial BP measurement. BP (systolic and diastolic) was measured once a minute during test and recovery periods, including at the maximum workload, immediately after the maximum workload, immediately after the end of the test, and after 5 min of recovery. Heart rate was measured with continuous ECG recording throughout the test and recovery periods. We assessed the absolute maximum power output (MPO) of the athletes as well as the MPO adjusted to individual body weight. Other measurements included maximum heart rate and heart rate at rest and 5 min after the exercise test.

Increases in systolic and diastolic BP were calculated from peak and baseline (resting) values and determined as blood pressure response (BPR). Further, the workload-adjusted BPR was calculated via maximum systolic BP/MPO. Pulse pressure was calculated as systolic—diastolic BP at rest and at maximum exercise conditions. In addition, mean BP was determined as: diastolic BP + (systolic BP-diastolic BP)/3.

Statistical analysis

Descriptive analyses were carried out on all study variables for the total sample. Further, descriptive statistics were used on all study variables by 25-OH vitamin D status (with < 30 ng/mL classified as "insufficient" and ≥ 30 ng/mL regarded as "sufficient"). All data are presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to determine normal distribution. In case of skewed distribution of the data, all analyses were performed on normalized data. Between-group comparisons (insufficient vs. sufficient 25-OH vitamin D levels) were made using independent sample *t* tests. Bivariate relations were analysed using Pearson's product-moment correlation coefficient. Statistical significance was set at $p < 0.05$ (two-tailed) for all measurements. All statistical analyses were performed using the statistical software SPSS 25.0 for Mac (Statistical Package for the Social Sciences, Chicago, IL, USA).

Results

Cohort characteristics

The 120 professional handball and ice hockey athletes (mean age of 25.8 ± 5.2 year) included in the study were experienced athletes and had participated in professional training for 9.6 ± 5 year with a current mean training time of 17.5 ± 3.0 h per week. The height was 189.9 ± 7.2 cm and the mean weight was 92.9 ± 10.6 kg, resulting in mean body mass index of 25.7 ± 1.85 kg/m^2 (Table 1).

The mean 25-OH vitamin D level of the 120 athletes was 37 ± 11.9 ng/mL. Eighty-five athletes (71%) displayed sufficient vitamin D levels of ≥ 30 ng/mL and 35 (29%) were found to be vitamin D insufficient (< 30 ng/mL). There were no significant between-group differences in age and characteristics. As expected, the 25-OH vitamin D levels between the sufficient and insufficient groups (42.3 ± 8.9 ng/mL vs. 22.95 ± 5.1 ng/mL) were different ($p < 0.001$). Table 2 shows the between-group comparison for all parameters measured.

Table 1 Characteristics of all 120 professional indoor athletes

	Mean	SD
Age (years)	25.8	5.2
Height (cm)	189.8	7.2
Weight (kg)	92.9	10.6
Body mass index (kg/m^2)	25.7	1.85
History of training (years)	9.6	5
Training per week (h)	17.5	3

25-OH vitamin D and resting blood pressure

The mean systolic/diastolic BP in all 120 athletes was 121 ± 10/75 ± 7 mmHg. The level of 25-OH vitamin D was positively correlated with systolic BP ($r^2 = 0.186$, $p = 0.045$), whereas 25-OH vitamin D level and diastolic BP were not correlated ($r^2 = -0.10$, $p = 0.28$). Further, there was a positive correlation of 25-OH vitamin D level and pulse pressure at rest ($r^2 = 0.209$, $p = 0.024$). None of the other measured BP parameters correlated with the 25-OH vitamin D status (Table 3).

There were no differences in resting systolic and diastolic BP, pulse pressure, and mean BP between athletes with insufficient and sufficient 25-OH vitamin D levels. Detailed data are given in Table 2.

25-OH vitamin D and blood pressure response during maximum exercise

The mean maximum BP in all athletes was 193 ± 21/80 ± 7 mmHg, with a mean systolic BP increase of 72 ± 22 mmHg and a mean diastolic BP increase of 4 ± 6 mmHg. The maximum pulse pressure was 113 ± 18 mmHg.

Athletes with sufficient 25-OH vitamin D levels had a higher maximum systolic BP compared with those with insufficient levels (198 ± 17 vs. 189 ± 19, $p = 0.026$). In addition, the maximum pulse pressure (118 ± 18 vs. 109 ± 21 mmHg, $p = 0.021$) was higher in athletes with sufficient 25-OH vitamin D levels, whereas the individual BPR was not different between groups (76 ± 20/5 ± 6 vs. 69 ± 22/3 ± 6 mmHg, $p = 0.103$). Detailed data are given in Table 2. In the total sample, 25-OH vitamin D levels did not correlate with any of the exercise-induced changes in BP (Table 3).

25-OH vitamin D and performance

All athletes completed the maximum exercise test until exhaustion and a maximum heart rate above the calculated individual 85% threshold (of individually calculated maximum heart rate). The mean maximum heart rate in all athletes was 184 ± 8 bpm and the mean workload was 349 ± 85 W with a corresponding maximum power output (MPO) of 3.77 ± 0.85 W/kg. The workload-adjusted BPR, calculated via maximum systolic BP/MPO, was 53.5 ± 12 mmHg × kg/W. Levels of 25-OH vitamin D correlated positively with maximum workload ($r^2 = 0.373$, $p < 0.001$) as well as maximum power output ($r^2 = 0.327$, $p < 0.001$), whereas 25-OH vitamin D levels and the

Table 2 Comparison of the different characteristics according to 25-OH vitamin D levels

	25-OH vitamin D levels				*p* value
	≥ 30 ng/mL		< 30 ng/mL		
	n = 85		*n* = 35		
	Mean	SD	Mean	SD	
25-OH vitamin D (ng/mL)	42.3	8.9	22.95	5.1	**< 0.001**
Age (years)	25.5	4.8	27.5	5.8	0.063
Weight (kg)	92.5	10.5	94	11	0.505
Height (cm)	189.6	7.0	190	8.1	0.661
BMI (kg/m^2)	25.7	1.9	25.9	1.5	0.611
Body surface area (m^2)	2.2	0.15	2.22	0.17	0.532
Heart rate at rest (bpm)	58.4	10.5	59.1	9.4	0.748
Brachial systolic blood pressure (mmHg)	122.1	10	120	11.6	0.333
Brachial diastolic blood pressure (mmHg)	75.1	7.4	76.8	8.6	0.362
Mean brachial blood pressure (mmHg)	91	6.3	90.7	6.5	0.862
Brachial pulse pressure (mmHg)	47	11	43.5	13.3	0.152
Maximum heart rate (bpm)	184	8.4	183.7	7.2	0.862
Maximum systolic brachial blood pressure (mmHg)	197.8	17.5	189.3	19.4	**0.026**
Mean maximum brachial blood pressure (mmHg)	116.7	8	119.1	8.2	0.169
Increase from resting systolic blood pressure (mmHg)	75.7	20	69.3	21.6	0.103
Brachial pulse pressure exercise (mmHg)	118	18	108.9	20.8	**0.021**
Maximum diastolic brachial blood pressure (mmHg)	79.7	7.4	80.4	7.3	0.651
Increase from resting diastolic blood pressure (mmHg)	4.6	5.7	3.4	6.3	0.621
Maximum work load (W)	367.2	78.4	332.8	79.9	**0.039**
Maximum power output (MPO) (W/kg)	3.99	0.82	3.58	0.78	**0.015**
Max. systolic blood pressure/MPO (mmHg × kg/W)	51.3	10.2	55.5	14.1	0.079
Parathyroid hormone (pg/mL)	31.2	17.5	42.3	17.5	**0.003**
Calcium (mmol/L)	2.38	0.09	2.34	0.14	0.142
Magnesium (mmol/L)	0.82	0.05	0.82	0.06	0.713
Hemoglobin (g/dL)	14.9	1	15.1	0.85	0.402
Hematocrit (Vol%)	42.7	2.4	42.9	2.2	0.699

Bold text signifies significant differences. Values are given as means ± standard deviation (SD)

workload-adjusted maximum systolic BP ($r^2 = -0.222$, $p = 0.015$) were negatively correlated. All other exercise-induced BP measurements did not correlate with 25-OH vitamin D levels (Table 3).

As shown in Table 2, athletes with sufficient vitamin D levels had a higher maximum power output and achieved higher workloads than those with insufficient levels. The workload-adjusted BPR was not different between vitamin D-sufficient and -insufficient athletes. Maximum heart rate was also not different between the groups.

Linear regression analyses revealed that a higher level of 25- vitamin D ($p < 0.001$) is a statistically significant predictor of a higher maximum output ($r^2 = 0.123$, corrected $r^2 = 0.115$, $p < 0.001$, F(1120) = 16, Durbin-Watson statistic 2.123) and of a higher maximum workload ($r^2 = 0.126$, corrected $r^2 = 0.118$, $p < 0.001$, F(1120) = 16.5, Durbin-Watson statistic 2.065). Thus, 25- OH vitamin D levels were not able to predict the workload-adjusted BPR ($r^2 = 0.078$, corrected $r^2 = 0.070$, $p = 0.12$, F(1120) = 92.3, Durbin-Watson statistic 1.23).

25-OH vitamin D and blood parameters

Mean parathyroid hormone levels were 34 ± 18 ng/mL, calcium levels were 2.37 ± 0.11 mmol/L, and magnesium levels were 0.82 ± 0.05 mmol/L for all athletes. Mean haemoglobin levels were 15 ± 0.89 g/dL and the mean haematocrit was 42.8 ± 2.24%. We found a negative correlation of 25-OH vitamin D with parathyroid hormone ($r^2 = -0.330$, $p < 0.001$) and a positive correlation with calcium levels ($r^2 = 0.229$, $p = 0.013$). The other parameters tested did not correlate with the 25-OH vitamin D status (Table 3).

Athletes with insufficient 25-OH vitamin D levels displayed higher parathyroid hormone levels compared with athletes with sufficient vitamin D (42.3 ± 17.5 vs. 31.2 ± 17.5 ng/mL, $p = 0.003$). The other measured blood

Table 3 Spearman correlation coefficients for each variable for 120 athletes

Variable	Correlation with 25-OH Vitamin D Concentration	*p* value
Age	− 0.072	0.439
Weight	− 0.011	0.90
Height	− 0.052	0.577
BMI	0.049	0.594
History of training	− 0.032	0.733
Training per week	0.049	0.599
Resting heart rate	0.012	0.905
Systolic blood pressure	0.186	**0.045**
Diastolic blood pressure	− 0.101	0.280
Pulse pressure at rest	0.209	**0.024**
Mean brachial blood pressure	0.014	0.881
Maximum heart rate	0.081	0.387
Maximum systolic blood pressure	0.078	0.401
Maximum diastolic blood pressure	0.010	0.915
Pulse pressure exercise	0.095	0.308
Mean blood pressure exercise	0.071	0.527
Increase from resting systolic BP	− 0.026	0.777
Increase from resting diastolic BP	0.113	0.223
Increase from resting mean BP	0.059	0.527
Maximum workload	0.373	**< 0.001**
Maximum power output (MPO)	0.327	**< 0.001**
Maximum systolic BP/ MPO	− 0.222	**0.015**
Parathyroid hormone	− 0.330	**< 0.001**
Calcium	0.229	**0.013**
Magnesium	− 0.077	0.422
Hemoglobin	0.067	0.477
Hematocrit	0.014	0.877

Bold text signifies a significant correlation

parameters did not show differences between the two groups (Table 2).

Discussion

To the best of our knowledge, our study is the first to investigate the blood pressure response to a standardized maximum exercise test in professional indoor athletes in Germany and its correlation with 25-OH vitamin D status. Our main findings are that athletes with sufficient vitamin D levels displayed a higher maximum systolic BP and maximum pulse pressure during exercise compared with athletes with insufficient vitamin D levels. Further, the achieved maximum workload and MPO were higher in athletes with sufficient vitamin D levels. The BP increases during exercise (BPR) and the workload-adjusted BPR were not different between the sufficient and insufficient groups, however, indicating that the higher maximum systolic BP in sufficient athletes was caused by the better MPO. This assumption is underpinned by the lack of a correlation of vitamin D levels with both the maximum systolic BP and the BPR. Further, 25-OH vitamin D levels predicted maximum workload and MPO, but not the workload-indexed BPR.

These findings were surprising, since we hypothesized that athletes with insufficient vitamin D levels would display both a higher BP at rest and a higher BPR to a maximum exercise test compared with athletes with sufficient vitamin D levels. These assumptions were based on our own recently published research results in which we demonstrated that vitamin D-insufficient elite handball athletes displayed a higher peripheral and central BP than those with sufficient vitamin D levels (Bauer et al. 2019). Thus, contrary to our hypothesis, the current study showed that vitamin D levels were not associated with the BPR and the maximum BP during a maximum exercise. Athletes with sufficient vitamin D levels even had a higher maximum systolic BP than insufficient athletes, which was explained by the better performance of vitamin D-sufficient athletes.

Interestingly, the detected maximum systolic BP of our professional indoor athletes (193 ± 21 mmHg) was lower than that reported by Pressler et al. (Pressler et al. 2018), who found a mean maximum BP of 204 ± 22 mmHg in their male professional athletes. Accordingly, the mean increase from resting systolic BP was lower in our cohort than in theirs (72 ± 21 vs. 80 ± 20 mmHg), and the maximum diastolic BP was slightly higher in our cohort (80 ± 7 vs. 77 ± 9 mmHg) both in the total cohort and in the vitamin D-sufficient group. The study of Pressler at el. seems to be the most appropriate study to compare with ours, since their male cohort was of similar age and displayed a similar maximum heart rate (our study 184 ± 8 vs. Pressler et al. 186 ± 12 bpm) and a comparable MPO (3.77 ± 0.85 vs. 4.15 ± 0.61 W/kg). In addition, resting heart rate (59 ± 10 vs. 60 ± 11 bpm) and resting BP (122 ± 10/75 ± 7 vs. 124 ± 12/77 ± 7 mmHg) were comparable in the two study populations. Unfortunately, the lack of assessment of vitamin D levels in the report by Pressler et al. (Pressler et al. 2018) limits the comparison with our own results.

Another current study by Caselli et al. addressing the BPR to a maximum exercise test in Olympic athletes reported a maximum BP of 190 ± 20/75 ± 8 mmHg (Caselli et al. 2016), which is lower than the value we measured. Athletes performing "mixed exercise" demonstrated the highest resting BP in this study (Caselli et al. 2016), which is in line with other publications (Berge et al. 2015; Pressler et al. 2018; Hedman et al. 2019b). Further, male athletes have been shown to display a higher resting BP than females (Hedman et al. 2019b; Pressler et al. 2018; Berge et al. 2015). Our cohort, consisting of male handball and ice hockey players

can also be considered "mixed exercise" athletes. Unfortunately, the data presented by Caselli et al. for mixed sports are not divided by gender, which limits comparison. The maximum workload in this study (Caselli et al. 2016) was significantly lower compared to that of our group (268 ± 53 vs. 349 ± 85 W) and, in addition, the maximum heart rate was significantly lower (166 ± 10 vs. 184 ± 8 bpm). The mean age of 25 ± 6 years and the surprisingly low maximum heart rate raises the question whether the accomplished exercise test can be really considered to be a maximum exercise test. Further, lack of assessment of 25-OH vitamin D precludes correlation with vitamin D status and thus limits the comparison with our results.

Only a few studies have addressed the association of 25-OH vitamin D and BPR with exercise (Zaleski et al. 2019; Babur Guler et al. 2016). None, to the best of our knowledge, have examined professional athletes, a population that has been repeatedly reported to be vitamin D insufficient (Bauer et al. 2018; Owens et al. 2018, 2015). In 417 healthy adults (mean age 44), Zaleski et al. (Zaleski et al. 2019) reported that they found no difference in the BPR to a maximal exercise test and in the maximum BP between probands with insufficient and those with sufficient 25-OH vitamin D concentrations. Only 52% of the participants displayed normal resting BP, however, and 22.5% were considered to have established hypertension. Further, the cohort age was given as 20–76 years, data were not stratified by sex, and > 50% of the participants were females, who display a lower BPR than males (Zaleski et al. 2019). Therefore, these results cannot be meaningfully compared with the findings of our study. This previous study, however, was the first to examine the association of vitamin D levels with the BPR to exercise in a healthy population. Interestingly, the reported maximum BP in this investigation (Zaleski et al. 2019) was considerably lower than in our study and the studies of Caselli et al. (Caselli et al. 2016) and Pressler et al. (Pressler et al. 2018). This finding might be explained by the lower performance of the participants (VO2 max. 34 mL/kg × min), as a normal, healthy population was examined instead of athletes (Zaleski et al. 2019).

In our study, we identified a highly significant correlation of vitamin D levels and MPO. The influence of vitamin D on physical performance levels of male professional athletes has been described in several studies (Hamilton et al. 2014; Ksiazek et al. 2016), which can be explained via both its musculoskeletal and cardiovascular effects (Cannell et al. 2009; Owens et al. 2015; Wang 2016; Allison et al. 2015); however, the influence of vitamin D on the BPR to exercise was not examined in athletes thus far. The higher maximum BP that we measured in athletes with sufficient 25-OH vitamin D levels might be explained by a higher performance. It is known that higher exercise performance correlates with a higher BPR and higher maximum BP in athletes. Therefore, the workload adjustment in the BPR to exercise was proposed to identify athletes with an "exaggerated" BPR instead of using absolute cut-off values (Hedman et al. 2019a). Several mechanisms have been discussed to contribute to the excessive increase in BP during exercise, including aortic distensibility (Roman et al. 2007; Thijssen et al. 2016), endothelial dysfunction (Tzemos et al. 2009), and increased activation of the renin–angiotensin–aldosterone system (Schultz et al. 2013). Interestingly, all of these modifiers of the BPR to exercise are influenced by 25-OH vitamin D (Norman 2008; Tarcin et al. 2009; Christakos et al. 2013).

We could not detect correlations of vitamin D levels with BP changes under exercise conditions. This might be explained by the excellent fitness of our professional athletes, since it is possible that vitamin D and physical fitness differentially affect the cardiovascular system and the BPR to exercise, with measurable differences only in individuals who cannot compensate for the deleterious effects of vitamin D insufficiency (Norman 2008; Tzemos et al. 2009). Today, the ability to examine vascular function and central haemodynamic parameters including central BP (cBP) via non-invasive tools might offer new opportunities to reveal the influence of 25-OH vitamin D on BP and the BPR to exercise in an athletic population (Bauer et al. 2019). cBP is determined by the complex interaction between aortic compliance, elasticity and the resistance arteries' ability to channel blood flow in accordance with tissue needs (Stephen Hedley and Phelan 2017). Hence, cBP is superior to brachial blood pressure in identifying changes in vascular functional parameters (Hodson et al. 2016) and cardiovascular risk (Williams et al. 2006; Roman et al. 2007; Cheng et al. 2013; Fan et al. 2016; Herbert et al. 2014). Particularly in young men, central diastolic BP, but not peripheral systolic pressure, is a predictor of cardiovascular risk (Wilkinson et al. 2001). Therefore, further studies that investigate the impact of 25-OH vitamin D on vascular function, cBP, and the BPR to exercise in athletes are needed.

Overall, the clinical importance of the BPR to exercise and maximum systolic BP is obvious, as it has been shown that a high BPR to exercise predicts future development of hypertension in young athletes (Caselli et al. 2019) as well as the normal population (Tzemos et al. 2015; Percuku et al. 2019; Schultz et al. 2015). Athletes are more frequently exposed to exercise-induced high BP than sedentary individuals, and exercise testing is frequently performed in the cardiovascular evaluation of competitive athletes (Hedman et al. 2019b). Therefore, reliable cut-off values have to be established and, given the workload-dependent BPR to exercise, a workload-adjusted approach instead of using absolute cut-off values might be a good strategy for identifying athletes with an exaggerated BPR (Hedman et al. 2019a). Thus far, insufficient 25-OH vitamin D levels do not appear to be

a risk factor for an exaggerated BPR to a maximum exercise test in professional male indoor athletes.

Limitations

Our study has a few noteworthy limitations. The number of participants limited its power to uncover potential correlations between 25-OH vitamin D status and markers of cardiac and vascular function other than brachial BP and the BPR to a maximum exercise test. The focus on professional indoor handball and ice hockey players may limit extrapolation of the results to other sport disciplines; however, as these team sports expose athletes to the haemodynamic stress of frequent interval sprints, they are representative of other sports with a high dynamic component (> 75% VO2max) and a moderate static component (10–20%) (Levine et al. 2015). A further limitation is our exclusive focus on male athletes, which precludes the extrapolation of our results to female athletes. We are currently addressing all three issues by extending our research to include larger numbers of professional male and female athletes from various sports disciplines.

Conclusion

We have shown for the first time that professional male handball and ice hockey players with sufficient 25-OH vitamin D levels display a higher maximum systolic BP during a maximum exercise test than do athletes with insufficient 25-OH vitamin D levels. This difference was an expression of a significantly higher MPO in vitamin D-sufficient athletes, highlighting the impact of vitamin D on physical performance of these athletes. Thus, the BPR between athletes with sufficient 25- OH vitamin D levels compared to those with insufficient levels was not different. Further, in both groups of athletes, the BPR to a maximum exercise did not exceed the currently proposed thresholds for athletes.

We suggest that highly- trained athletic populations present a unique opportunity to address the modifying effects of cardiorespiratory fitness on the association of 25-OH vitamin D with cardiovascular risk markers. Our results may serve to stimulate future investigations into the correlation of vitamin D with parameters of vascular function and central haemodynamic parameters.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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Impact of Vascular Function on Maximum Power Output in Elite Handball Athletes

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ABSTRACT

Purpose: To evaluate vascular function and its relationship to cardiorespiratory fitness in professional handball athletes. **Method**: We examined 30 male professional handball athletes (age 27 ± 4 y) and 10 male sedentary controls (age 26 ± 5 y) at rest. The workup included exercise testing via ergometry. To assess vascular function, a validated electronic model of the arterial tree (vasc assist 2®) was used. It replicates noninvasively acquired pulse pressure waves by modulating the relevant functional parameters of compliance, resistance, inertia, pressure, and flow. The maximum oxygen uptake (VO2max) was estimated using the validated heart rate ratio method. **Results**: Athletes had a significantly lower systolic and diastolic central blood pressure (cBP) compared to controls (102 ± 9/60 ± 9 vs. 110 ± 8/74 ± 9 mmHg, $p < .01$), whereas aortic pulse wave velocity (PWV) (6.2 ± 0.8 vs. 6.3 ± 0.5 m/s, $p = .45$) and augmentation index at a heart rate of 75 (Aix@75) (−4 ± 12 vs. −13 ± 16%, $p = .06$) were not different. Resistance index (R) (15.9 ± 4.4 vs. 10.6 ± 0.6, $p = .001$) and maximum power output (MPO) (3.55 ± 0.54 vs. 2.46 ± 0.55 Watt/kg, $p < .001$) were significantly higher in athletes compared to controls. We found no relevant correlation between MPO, resting heart rate, PWV, Aix@75, and cBP. A higher VO2max ($p = .02$) and a lower R ($p < .01$) were significant predictors of a higher MPO in athletes. **Conclusion**: R had an independent and strong correlation to MPO in athletes, which might help to disentangle the contribution of aerobic capacity and arterial function to physical power.

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Regular exercise performed at moderate intensity decreases cardiovascular and overall mortality and therefore constitutes a cornerstone in preventive medicine (Lee et al., 2012). The improvement of cardiorespiratory fitness is currently seen to be the key factor in this setting (Davidson, Vainshelboim, Kokkinos, Myers, & Ross, 2018; Lee, Artero, Sui, & Blair, 2010), as it is known that decreased exercise capacity is associated with increased mortality (Lee et al., 2010).

The characteristics of sports-related adaptations of the heart are now well established (Baggish, 2016; Petek & Wasfy, 2018; Weiner & Baggish, 2012) and include structural, neurohumoral, autonomic, and metabolic mechanisms (Baggish, 2016; Weiner & Baggish, 2012). Cardiac remodeling among athletes has been investigated thoroughly, leading to the term "athlete's heart" (Baggish, 2016; Petek & Wasfy, 2018). The upper limit of exercise, however, is frequently questioned, suggesting that high amounts of intensive exercise may be harmful. (La Gerche et al., 2012; La Gerche & Heidbuchel, 2014). Intensive bouts of exercise were shown to cause temporary acute functional and biochemical cardiac dysfunction with unclear significance (La Gerche et al., 2012). In line with these findings, an unexpectedly high incidence of atherosclerosis in endurance athletes was reported (Merghani et al., 2017). These studies encouraged the discussion of sports-related cardiovascular damage in professional athletes (La Gerche & Heidbuchel, 2014).

Interestingly, despite intensive research efforts aimed at cardiac adaptations, little is known about exercise-induced adaptations of the vascular system (Green, Hopman, Padilla, Laughlin, & Thijssen, 2017; Green & Smith, 2018). The aorta in particular is exposed to great hemodynamic stress during prolonged intensive exercise and must withstand a substantial elevation of central blood pressure (cBP). Concurrently, the integrity of the aortic reservoir function must be maintained to ensure adequate coronary perfusion (Stephen Hedley & Phelan, 2017).

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Resistance arteries are an additional crucial factor for the regulation of blood flow during exercise (Stephen Hedley & Phelan, 2017).

The role of arterial stiffness in the development of cardiovascular disease has been demonstrated in several studies (Mitchell, 2009; Roman et al., 2007). A loss of distensibility in the central elastic arteries compromises their ability to buffer the ejected blood volume from the left ventricle. This leads to an increase in cBP and compromised coronary flow (Roman et al., 2007; Thijssen, Carter, & Green, 2016), which constitutes an increased risk for cardiovascular events (Fan et al., 2016; Roman et al., 2007). This effect is amplified if peripheral arteries display elevated arterial stiffness (Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014). An early return of the reflected pressure wave contributes to increases in cBP and arterial wall stress (Green & Smith, 2018; Kaess et al., 2012).

In this context, it is obvious how a mismatch between cardiovascular functional integrity, secondary to atherosclerotic load and other aortic pathologies, and the demands placed by exercise on the heart and vasculature may expose the exercising athlete to an increased risk of a sudden cardiovascular event (Merghani et al., 2017). With only 0–3.1% of sudden cardiac deaths in athletes being attributable to acute aortic pathologies (Stephen Hedley & Phelan, 2017), the role of concealed cardio-arterial dysfunction as a potential predictor of sudden cardiac events in athletes has become a valid and important subject of research (Merghani et al., 2017; Stephen Hedley & Phelan, 2017). It is fuelled by the contradictory results of investigations about the effects of intensive endurance exercise on arterial stiffness and cBP (Green et al., 2017; Okamoto, Min, & Sakamaki-Sunaga, 2018; Peres et al., 2018; Sardeli, Gaspari, & Chacon-Mikahil, 2018; Staniszewska, Pudlo, Ryterska, & Stachowska, 2016; Vlachopoulos et al., 2010).

Recently, a new noninvasive diagnostic tool (vascassist2®) (Schumacher, Kaden, & Trinkmann, 2018) has been validated for analyzing pulse pressure waves in order to assess arterial stiffness, cBP, and vascular resistance. This method might help to reveal the impact of professional sports on cardiovascular adaptations and its relationship to cardiorespiratory fitness. Here we employed this tool in a pilot study to examine the effects of professional sports on vascular function in male professional handball players. Furthermore, we hypothesized that measurable vascular function correlates with the maximum power output (MPO) of these athletes.

Methods

Participants

The participants were 30 healthy male professional handball players of the first German division and 10 healthy male sedentary controls. All participants gave their written informed consent and filled out a questionnaire regarding health status, medication, nutrition supplementation, training, and competition history. The physical assessment of the athletes took place after a six-week, competition-free period as part of a regular preseason medical checkup. Controls were examined in spring. All participants underwent a physical examination, blood testing, electrocardiogram (ECG) at rest, and echocardiography.

Study design

This is a cross- sectional, single-center pilot study. All the procedures were performed between 9:00 a.m. and 12:00 p.m., at a constant room temperature of 22 degrees Celsius.

Exercise testing

A progressive maximal cycling ergometer test with concurrent blood pressure and ECG recording was performed (Schiller AG®, Switzerland). The exercise test protocol of the athletes started with a load level of 100 W after a 2-min warm-up period, which was conducted with 50 W. Controls started with 50 Watt after a warm up period conducted with 25 Watt. Loads were increased by 50 W in athletes and 25 Watt in controls every 2 min until exhaustion, which was defined as the participants' inability to maintain the load for 2 min. Next, the load was decreased to 25 W for 3 min of active recovery, followed by a cool-down period at rest of 2 min. The test concluded with a final ECG recording and a brachial blood pressure measurement. We assessed the MPO of the participants, maximum heart rate, heart rate at rest and after the exercise test, and systolic and diastolic brachial blood pressure at rest and during exercise. The VO2max was estimated using the validated heart rate ratio method (Uth, Sorensen, Overgaard, & Pedersen, 2004).

Noninvasive assessment of peripheral and central blood pressure and pulse pressure waveforms

We used the noninvasive vascassist2® device (isymed GmbH, Butzbach, Germany) to acquire pulse pressure waveforms by means of oscillometry. The device uses

a validated model (Schumacher et al., 2018) of the arterial tree, which consists of 721 electronic circuits representing all central and peripheral arterial sections. By modulating the circuits' capacitance, resistance, inductance, and voltage, the system replicates an individual's acquired pulse pressure waves. The system is based on the premise that the parameters used to replicate the pulse pressure waves are a quantitative representation of the functional parameters that gave rise to the pulse pressure wave in the biological original. The vascassist2® system is currently unique in the use of genetic algorithms to optimize the fidelity of the of pulse pressure wave replication (Schumacher et al., 2018). Fidelity replications of 99.6% or above were included in the analysis.

The noninvasive vascular evaluation was performed before the exercise testing in all athletes. After a 15-min rest, measurements were performed in a supine position using four conventional cuffs adapted to the arm and forearm circumference of the athletes. Radial and brachial pulse pressure waves were acquired on both arms with step-by-step deflation of the cuffs. The measurements took place in a room with a comfortable temperature of 22°C and a lack of external stress influences. Participants were advised not to move during the acquisition of pulse pressure waves. Two brachial and three radial measurements were performed to guarantee stable and valid results. The total duration of the examination was 15 min. The acquired pulse pressure waves then were analyzed with a validated electronic model of the arterial tree to assess vascular functional parameters. Brachial and radial systolic and diastolic blood pressure, central systolic and diastolic blood pressure, aortic pulse wave velocity (PWV), augmentation index (Aix), augmentation index at a heart rate of 75 bpm (Aix@75), resistance index, and ejection duration were calculated. cBP was determined with a transfer function that was based on the peripheral arterial waveform. Calculation of Aix@75 was also based on the pulse waveform.

Statistical analysis

Data are presented as mean ± standard deviation (SD) in case of normal distribution of the data. The Shapiro-Wilk test was used to determine normal distribution. In case of skewed distribution of the data, data are given as median and interquartile ranges. Between-group comparisons were performed using independent-samples t-tests. Bivariate relations were analyzed using Spearman correlation coefficient. Pearson's correlation was used to determine linear correlations between vascular functional parameters and maximum power output, assessed by ergometer and displayed as Watt/kg. Linear regression was performed to evaluate maximum power output as a function of resistance index.

Statistical significance was set at $p < .05$ for all measurements. All statistical analyses were performed using Stata Statistical Software: Release 15. (StataCorp. 2017. College Station, TX: StataCorp LLC).

Results

We included 30 professional male handball players (mean age of 27 ± 4 y) and 10 healthy, age- matched, male sedentary controls (26 ± 4 y). Neither age ($p = .65$) nor body mass index ($p = .58$) were significantly different between the two groups. In contrast, height ($p < .001$) and weight ($p = .02$) were significantly higher in handball athletes.

The height of handball players was 191 ± 4.7 cm and the mean weight was 94.2 ± 10.7 kg, resulting in mean body mass index of 25.7 ± 2.3 kg/m^2. The players had participated in professional training for 10.7 ± 4.3 years and had a mean training time of 17.1 ± 1.1 hours per week.

The height of the male controls was 182 ± 7.8 cm and the mean weight was 82.8 ± 10.2 kg, mean body mass index was 25 ± 2.6 kg/m^2. The controls were non-athletes with a mean training time of 0.3 ± 0.3 hours per week.

Three athletes and two controls were current smokers, and none of the participants suffered from cardiovascular diseases. All participants were free from any medication. Twelve athletes used nutrition supplementation with magnesium and protein shakes on an irregular basis.

The mean resting heart rate was 53 ± 7 bpm in athletes and 74 ± 13 bpm in non- athletes. ($p < .001$). Resting brachial blood pressure was 123 ± 8 mmHg systolic and 61 ± 9 mmHg diastolic in athletes and 129 ± 9 mmHg systolic and 74 ± 9 mmHg diastolic in controls. Both the systolic ($p = .02$) and the diastolic blood pressure ($p < .001$) at rest were significantly higher in non-athletes compared to athletes.

Athletes had a significantly lower systolic and diastolic central blood pressure (cBP) compared to controls (102 ± 9/60 ± 9 vs. 110 ± 8/74 ± 9 mmHg, $p < .01$), whereas aortic pulse wave velocity (PWV) was not different between groups (6.2 ± 0.8 vs. 6.3 ± 0.5 m/s, $p = .45$). The augmentation index at a heart rate of 75 (Aix@75) was determined to be −4 ± 12% in athletes and −13 ± 16% in controls ($p = .06$). Resistance index (R) was significantly higher ($p = .001$) in handball athletes (15.9 ± 4.4) compared to non- athletes (10.6 ± 0.6).

The mean maximum heart rate during the exhaustive exercise test was significantly ($p < .001$) lower in athletes (172 ± 10 bpm) compared to controls (188 ± 10 bpm). The mean test duration was 18 min 46 sec ± 2.5 min in athletes and 10 min 27 sec ± 3.5 min in controls ($p < .001$). Athletes achieved a significant ($p < .001$) higher maximum load (343 ± 77 W) compared to controls (203 ± 24 W) with a corresponding higher MPO (3.55 ± 0.54 W/kg vs. 2.46 ± 0.55 W/kg, $p < .001$). All participants completed the test without any symptoms and normal electrographic findings. Non-athletes displayed a significantly ($p = .044$) higher maximum systolic brachial blood pressure during the exercise test compared to athletes (203 ± 24 vs. 189 ± 17.5 mmHg), whereas maximum diastolic blood pressure was not different (92.6 ± 9.4 vs. 89.9 ± 8.5 mmHg). Detailled data of the vascular evaluation are given in Table 1.

We used Spearman's correlation coefficient to determine whether there were correlations between MPO values and participants´ demographics. We found no significant correlations between anthropometric data, history of training, or amount of training per week and the MPO.

Conversely, the correlation between maximum power output and resistance index was highly significant ($r = -0.597$, $p < .01$) in athletes, but not in the group of sedentary controls.

Similarly, there was a significant correlation between maximum power output and VO2max ($r = -0.445$, $p = .019$) only in the athletic group.

We found no statistically significant correlation between maximum power output and resting heart rate, central diastolic blood pressure, mean central blood pressure, pulse wave velocity and Aix@75 both in athletes and sedentary controls. The results of the athletic population are presented in Table 2.

Table 2. Spearman correlation coefficients for each variable.

Variable	Correlation with MPO	*p* values
Resistance Index	−0.5335	.0042*
VO2max	0.4455	.0199*
Resting Heart Rate	−0.3100	.1156
Aortic Syst. BP	−0.3620	.0635
Aortic Diast. BP	−0.1971	.3245
Mean Aortic BP	−0.2405	.2269
Aix@75	−0.3553	.0689
PWV	−0.2221	.2656

*statistically significant correlation ($p < .05$).

Linear regression analysis revealed that a lower resistance index ($p = .01$) is a statistically significant ($r^2 = 0.27$, $p = .005$) predictor of a higher maximum power output in male professional handball athletes explaining 27% of the variance in maximum power output. The regression result is shown in Figure 1.

Univariate linear regression analyses revealed that resistance index and aerobic capacity individually and significantly predicted maximum power output in handball athletes. However, in bivariate linear regression with resistance and VO2max as predictors, only VO2max remained statistically significant (Table 3).

Discussion

This is the first study to evaluate vascular function, cBP, PWV, and aortic augmentation index in professional handball players in Germany. Furthermore, we are the first to investigate the relationship of these parameters to handball athletes' physical performance, assessed as MPO. The novel finding of our study is the inverse correlation of resistance index with a higher MPO in these athletes, as determined by an exhaustive exercise test. Further, central blood pressure was significantly lower in athletes at rest compared to sedentary controls. These findings emphasize the link between vascular function and physical performance in these athletes. The lower central blood pressure

Table 1. Results of vascular evaluation and exercise testing in athletes ($n = 30$) and controls ($n = 10$).

	Athletes $n = 30$		Controls $n = 10$		
	Mean	*SD*	Mean	*SD*	*p* value
Resting Heart Rate (bpm)	53	7	74	5	.01
Brachial systolic blood pressure (mmHg)	123	8	129	9	.02
Brachial diastolic blood pressure (mmHg)	61	9	74	9	<.001
Mean aortic blood pressure (mmHg)	74	8	88	10	<.001
Aortic systolic blood pressure (mmHg)	102	9	110	8	.01
Aortic diastolic blood pressure (mmHg)	60	9	74	9	<.001
Aortic pulse pressure (mmHg)	42	6.5	36	4.4	<.01
Aortic pulse wave velocity (m/s)	6.2	0.82	6.3	0.48	.45
Augmentation index @75 bpm (%)	− 4	12	−13	15	.06
Resistance index	15.88	4.43	10.66	2.04	<.001
Maximum power output (Watt)	343	77	202	43	<.001
Maximum power output (Watt/kg)	3.55	0.54	2.46	0.55	<.001
VO2max (est.mlO_2/kg*min)	50.88	6.8	37.4	5.1	<.001
Maximum systolic blood pressure (mmHg)	189	18	203	24	.04
Maximum diastolic blood pressure (mmHg)	89	8	93	9	.24
Maximum heart rate (bpm)	172	10	188	10	<.001

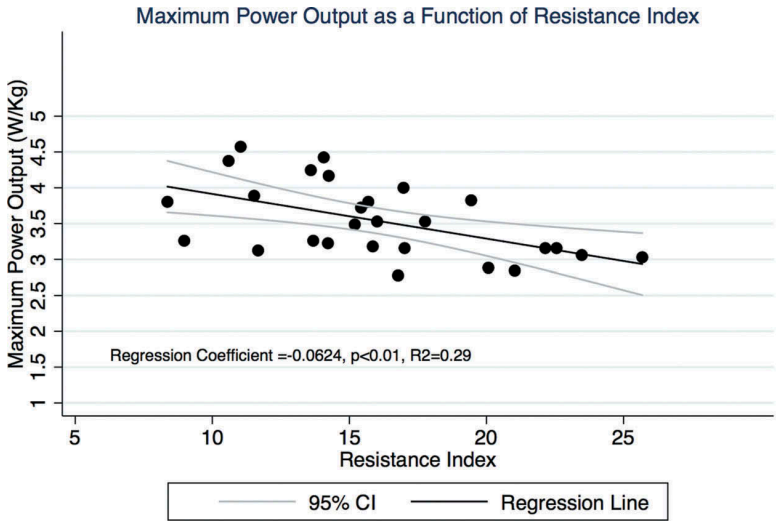

Figure 1. Maximum power output as a function of resistance index in handball athletes.

Table 3. Regression analysis of MPO over resistance index and VO2 max.

	(Model 1)	(Model 2)	(Model 3)
	b/SE	b/SE	b/SE
Resistance Index	−0.062**		−0.049*
	(0.020)		(0.021)
VO2max		0.034*	0.021
		(0.014)	(0.014)
Cons	4.538**	1.808*	3.266**
	(0.329)	(0.701)	(0.898)
R-squared	0.285	0.198	0.347

Note. Standard errors are in parenthesis
** $p < .01$, * $p < .05$

in professional athletes compared to age- matched controls might be the result of exercise- induced vascular adaptations. Interestingly, the age- matched sedentary controls displayed a lower resistance index at rest compared to athletes. Though, resistance index was not associated to a higher MPO in controls, but in athletes. One might speculate that these findings represent an improved vascular function in athletes, which contributes to a better performance under exercise conditions. Given the fact that maximum blood pressure was significantly lower in athletes compared to controls, emphasizes this assumption.

Our decision to investigate the relative predictive contributions of VO2max and resistance was driven by the fact that VO2max is a well-established and substantial predictor of power output. Since individuals with higher aerobic capacity tend to deliver higher power outputs (per kilogram bodyweight), the univariate regression model offers no way to tell us whether resistance may explain variability in MPO that VO2max could not also explain.

The result of our bivariate regression strongly supports the hypothesis that resistance, being a physical parameter of arterial function, has an independent and strong correlation with MPO, and may therefore help to disentangle the contributions of aerobic capacity and arterial function to physical power in athletes.

Denham et al. (Denham et al., 2016) showed in their study that Aix@75, but not cBP or PWV, was inversely correlated with the VO2 peak in endurance athletes. Athletes with the lowest Aix@75 possessed a higher VO2 peak, and the VO2 peak emerged as an independent predictor of Aix@75 (Denham et al., 2016). Therefore the authors concluded that Aix@75 plays a role in the cardiorespiratory fitness of endurance athletes (Denham et al., 2016). In our cohort of professional handball athletes, we did not detect statistically significant correlations of Aix@75, cBP, and PWV with MPO. Interestingly, the determined Aix@75 was even lower in the sedentary control group. Though, it was associated with maximum power output in this group, too. The different groups of athletes and sports examined might explain this difference.

Our cohort consisted of professional handball players. Handball is a team sport with many interval sprints. It was classified as a sport with a high dynamic component (>75% VO2max) and a moderate static component (10–20%) (Levine et al., 2015). The participants in the study of Denham et al. (Denham et al., 2016) were recreational endurance athletes with both a significantly lower training volume and a lower mean training history than our professional athletes. Furthermore, they were older than our athletes (33.5 vs. 27 years).

In healthy Asian males with a mean age comparable to that of our own study, carotid-femoral PWV was reported to be 8.53 m/s and Aix@75 4.7% (Okamoto et al., 2018). Unfortunately, no data about aortal PWV were presented,

which limits comparison with our results. Our participants were experienced elite athletes with a median professional training history of 10 years, which might have had an impact on our results. It is known that central arterial stiffness increases with age (Green & Smith, 2018) and that regular aerobic exercise is able to stop this ageing effect (Ashor et al., 2014; Green et al., 2017). This could partly explain the difference in PWV and Aix@75 between the studies (Staniszewska et al., 2016). Staniszewska et al. (Staniszewska et al., 2016) examined young male football and water polo athletes. Their athletes were younger than our participants (22 vs. 27 years), although they displayed a higher PWV (8.98 vs. 6.1 m/s) and a lower Aix@75 (−11 vs. −4%) than our handball players. The type of exercise is crucial to the interpretation of the studies, as aerobic exercise was shown to have the greatest impact on arterial stiffness (Ashor et al., 2014; Green & Smith, 2018). In marathon runners who were older than our athletes (38 vs. 27 years), a PWV of 6.89 m/s was measured that is only slightly higher than in our investigation (6.2 m/s) (Vlachopoulos et al., 2010). Though, the measured PWV of our age- matched sedentary control group was not significantly different compared to athletes.

Most studies in the literature used applanation tonometry from the carotid and femoral arteries to assess pule wave velocity and arterial stiffness, which is currently regarded as "gold standard" (Ashor et al., 2014). Though, the measurement technique is error-prone, as it requires a carefully adjusted transducer to obtain an accurate pulse wave (Massmann et al., 2017; Miyata, 2018). This may increase the stress in the patient being tested (Miyata, 2018). Recently, new validated methods to measure arterial stiffness and cBP have emerged that are able to evaluate vascular function noninvasively and simply via oscillometry in routine medical practice (Miyata, 2018). However, the characteristics and potential factors influencing the indices measured with the new methods need further investigation, and adequate cutoff values should also be established (Miyata, 2018).

Central blood pressure is more strongly related to vascular disease and outcome (Roman et al., 2007) than conventional brachial blood pressure, and therefore it has a greater prognostic value (Cheng et al., 2013; Fan et al., 2016; Herbert, Cruickshank, Laurent, Boutouyrie, & Reference Values for Arterial Measurements, 2014; Roman et al., 2007). Diagnostic thresholds for cBP measurements, derived from noninvasive tools, have been published recently: an optimal cBP of <110 mmHg systolic and <80 mmHg diastolic was proposed (Cheng et al., 2013). The threshold for arterial hypertension was calculated to be ≥130 mmHg/≥90 mmHg in this study (Cheng et al., 2013) and ≥124 mmHg/≥90 mmHg by Hulsen et al. (Hulsen et al., 2006). In another large study a normal systolic cBP of 103 mmHg was determined for healthy men aged 20–29 and 95 mmHg for healthy women, respectively (Herbert et al., 2014). In younger football and water polo athletes (mean age 22 years), a higher cBP (112/66 mmHg) was reported (Staniszewska et al., 2016). Our male elite athletes displayed a cBP of 102 mmHg systolic and 60 mmHg diastolic, which were lower than what was reported in these studies and lower than those measured in our age- matched healthy controls. Our professional athletes displayed a brachial blood pressure of 123/61 mmHg, which can be considered normal. The finding that the cBP is significantly lower than the brachial blood pressure is compatible with conditions for an increased coronary flow and thus for maintaining a higher cardiac performance (Green et al., 2017; Sardeli et al., 2018). Furthermore, it reflects the high compliance of the aorta in these athletes. The elastic properties of arteries are currently evaluated by employing pulse wave reflection and are expressed as the Aix.

A recently published meta-analysis revealed a significant reduction in PWV and Aix in endurance athletes compared with controls; this was not the case for resistance exercise (Ashor et al., 2014). The combination of aerobic and resistance exercise, which would best describe team handball in this context, also did not lead to a lowering of PWV and Aix (Ashor et al., 2014). However, as the authors of the meta-analysis pointed out, only two trials addressed the impact of combined exercise on PWV and Aix (Ashor et al., 2014). Furthermore, few studies report the measurement of heart-rate adjusted Aix (Ashor et al., 2014).

Young elite athletes are underrepresented in these analyses, as the majority of published studies examined the impact of exercise on older patients (>50 years) with cardiovascular diseases (Ashor et al., 2014). In young athletes participating in high intensity resistance training, there was even an increase in arterial stiffness observed, raising concerns about the cardiovascular safety of intensive resistance training (Miyachi, 2013).

Taken together, these contradictory results highlight the problems inherent to the use of surrogate markers for the determination of arterial function. The acknowledged gold-standard parameter PWV (Oh et al., 2017) is affected by heart rate and blood pressure (Tan, Butlin, Liu, Ng, & Avolio, 2012), but also by mechanical properties of the arterial wall, which vary across locations within the arterial tree (Townsend et al., 2015). Aix could theoretically serve as an indicator of the severity to which elevated PWV affects the heart by modulating afterload. However, it has been found that particularly in the case of negative Aix values (which characterizes our athlete population), this parameter fails as a quantifier of arterial function and should not be used for analyses (Hughes et al., 2013).

Correspondingly the ACCF/AHA and ESC do not recommend the use of PWV and Aix for routine risk screening in asymptomatic adults (Greenland et al., 2010; Vlachopoulos et al., 2015).

In contrast, determination of cardiorespiratory fitness significantly improves short-term and long-term prediction of cardiovascular mortality risk when added to traditional risk factors (Gupta et al., 2011; Ross et al., 2016). That in our athletic population we did not observe a correlation between MPO, PWV and Aix@75, while MPO was inversely correlated with resistance index, bespeaks the potential of using direct physical parameters of arterial function for the quantification of cardiovascular risk, even in apparently healthy populations.

Green et al. (Green et al., 2017; Green & Smith, 2018) hypothesized that global vascular resistance may be related to MPO in athletes. We found an inverse correlation between the resistance index and MPO in professional handball athletes, but not in the control group. Thus far, there exists no comparable tool for this index, which is derived from electrohydraulic analogy and a validated electronic model of the arterial tree (Schumacher et al., 2018).

The inability to obtain functional global vascular resistance using noninvasive methods is currently viewed to be a major problem (Green & Smith, 2018). Thus, surrogate markers like flow-mediated dilation are widely used to gain information about changes in vasodilator capacity in conduit arteries (Green et al., 2017). They mainly reflect the NO dilator pathway, but little is known about the prostaglandin-mediated vascular function, which constitutes a major limitation in the assessment of global vascular resistance in athletes (Green et al., 2017).

The newly introduced resistance index may help to reveal global vascular resistance, as its recording is independent of the user and can be performed with a very low assessment error (Massmann et al., 2017; Schumacher et al., 2018). However, the results of our study should be considered as hypothesis generating. This method to assess global vascular function in athletes should be independently validated in athletes of different sports and different intensities.

Limitations

Several limitations of this study should be mentioned. First, we did not address the underlying mechanisms in the development of arterial stiffness in athletes. Second, we did not perform follow-up measurements to detect vascular adaptations during the competitive season. Third, we estimated VO2max using the validated heart rate ratio method. We are aware that estimating maximal oxygen consumption typically suffers from considerable inaccuracy when derived from, and applied to, inhomogenous groups of individuals with large variances in body composition, age and training status. Given our athletes' high and comparable training volume and history it is reasonable to assume that the calculated aerobic capacity, while underestimating the actual capacity, is nevertheless a reasonably reliable basis for estimating the correlation between VO2max and arterial function.

Fourth, potential confounders like caffeine intake or changes in diet were not assessed. Finally, we acknowledge that the study cohort was limited to 30 athletes and 10 controls. However, we examined a homogeneous group of professional handball athletes, which strengthens our analysis despite the small study group.

Conclusion

In summary, noninvasive assessment of vascular function delivers new insights about cardiovascular adaptations in athletes. The newly introduced resistance index reflects global vascular resistance and predicted maximum power output in professional handball athletes.

What does this article add?

The adaptations of the vasculature in elite athletes and its impact on cardiovascular performance are poorly understood. Noninvasive assessment of vascular function by means of oscillometry, using direct physical parameters of arterial function, is a new and promising way to gain insights into this topic. This method might help to reveal the impact of professional sports on cardiovascular adaptations and its relationship to cardiorespiratory fitness. Furthermore, the potential of using direct physical parameters of arterial function for the quantification of cardiovascular risk, even in apparently healthy populations, is encouraged.

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Workload-indexed blood pressure response to a maximum exercise test among professional indoor athletes

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Abstract

Background: Exercise testing is performed regularly in professional athletes. However, the blood pressure response (BPR) to exercise is rarely investigated in this cohort, and normative upper thresholds are lacking. Recently, a workload-indexed BPR (increase in systolic blood pressure per increase in metabolic equivalent of task (SBP/MET slope)) was evaluated in a general population and was compared with mortality. We sought to evaluate the SBP/MET slope in professional athletes and compare it with performance.

Design: This was a cross-sectional study.

Methods: A total of 142 male professional indoor athletes (age 26 ± 5 years) were examined. Blood pressure was measured at rest and during a standardized, graded cycle ergometer test. We assessed the BPR during exercise, the workload, and the metabolic equivalent of task (MET). Athletes were divided into groups according to their SBP/MET slope quartiles (I <4.3; II 4.3–6.2; III >6.2–9; IV >9 mmHg/MET) and compared regarding systolic BP (sBP) and workload achieved.

Results: Athletes in group I ($n = 42$) had the lowest maximum sBP (180 ± 13 mmHg) but achieved the highest relative workload (4.2 ± 1 W/kg). With increasing SBP/MET slope, the maximum sBP increased (II ($n = 56$): 195 ± 15 mmHg; III ($n = 44$): 216 ± 16 mmHg) and the workload achieved decreased (II: 3.9 ± 0.7 W/kg; III: 3.3 ± 0.5 W/kg). The differences in sBP between these groups were significant ($p < 0.001$). None of the athletes were assigned to group IV (>9 mmHg/MET).

Conclusion: Athletes in the lowest SBP/MET slope quartile displayed the lowest maximum sBP but achieved a higher workload than athletes classified into the other SBP/MET slope groups. This simple, novel metric might help to distinguish a normal from an exaggerated BPR to exercise, to identify athletes at risk of developing hypertension.

Keywords

Exercise test, professional athletes, indoor sports, performance, workload-indexed blood pressure, blood pressure response, hypertension

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Introduction

Healthy individuals with normal blood pressure (BP) at rest but an exaggerated BP response (BPR) during exercise are reportedly at higher risk of developing arterial hypertension.[1–3] In addition, a recent meta-analysis revealed that exercise-induced systolic BP (sBP) ≥196 mmHg predicted cardiovascular events with a sensitivity of 62% and a specificity of 75%.[4] Further, in men without a history of cardiovascular disease, a heightened risk of sudden cardiac death

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associated with an exaggerated systolic BPR to exercise testing (≥210 mmHg) was reported.[5]

In contrast, other studies concluded that a high peak exercise sBP was associated with a lower risk of future cardiovascular events and mortality,[3,6] and the sBP at maximum exercise was not found to be associated with increased rates of cardiovascular events.[7] Further, a lower exercise BP was found to be an independent predictor of cardiovascular events and mortality.[8]

Therefore, the clinical impact of BPR during exercise remains a controversial issue,[9,10] and upper reference values have not been established.[7,11–13] The European Society of Cardiology states in its latest guideline that there is currently no consensus on normal BPR during exercise.[14] In previous guidelines, a systolic peak BP of 210 mmHg for men and 190 mmHg for women were proposed as diagnostic thresholds for the general population.[15] Recommendations for athletes are lacking in both guidelines, yet recently published studies proposed different thresholds for defining an exaggerated BPR to exercise in athletes.[16,17] A higher exercise-induced BPR in athletes was explained as representing a superior exercise performance compared with that of the general population.[18] Thus far, the clinical relevance of BPR in athletes is unclear, although a higher risk of developing arterial hypertension in these athletes was suggested.[16] Further, in competitive triathletes, an exaggerated BPR to exercise testing was associated with a higher prevalence of myocardial fibrosis,[19] raising concerns about potential arrhythmic consequences, including sudden cardiac death.[20]

Regarding the physiological linear relationship between sBP and external workload via cardiac output, a higher sBP response to maximum exercise is observed in individuals with a high level of physical fitness.[16] In addition, a higher cardiorespiratory fitness improves survival and lowers the risk of cardiovascular events.[21] However, upper limits of a normal BPR to exercise need to be defined, and considering the specific workload instead of using absolute thresholds might help to distinguish normal from exaggerated BPR to exercise. The guidelines of the American College of Sports Medicine (ACSM) propose a normative increase of 10 mmHg of sBP per metabolic equivalent of task (MET).[22] Recently, these values were questioned,[13] and Hedman et al. found an increase in sBP per increase in MET (SBP/MET slope) of >6.2 mmHg/MET to be associated with a 27% higher risk of mortality over 20 years in males (mean age 59 years) with a high fitness level compared with those with a SBP/MET slope of <4.3 mmHg/MET.[3] The authors concluded that the calculated SBP/MET slope, as a workload-indexed measure of the relationship of systolic BPR to exercise, may be of prognostic value in subjects with higher fitness levels.[3] However, the SBP/MET slope has thus far not been investigated in elite athletes.

Therefore, this study was undertaken to characterize the SBP/MET slope and its association with the BPR to a maximum exercise test in male elite indoor athletes referred for clinical investigation. Both handball and ice hockey, with their many interval sprints, are team sports that expose athletes to high haemodynamic stress. Both were classified as a sport with a high dynamic component (>75% maximum oxygen uptake VO_2max) and a moderate static component (10–20%).[23]

Methods

Study design

The study was conducted as a cross-sectional study of professional athletes during the routine pre-season medical monitoring program of the first German handball division and the second German ice hockey division. Data were collected in the second half of July in the years 2015 to 2019 after a six-week competition-free interval. All participants received a clear explanation of the study and provided their written informed consent. The local ethics committee of the University of Giessen approved the study protocol. The study meets current ethical standards.[24]

Study population

The participants were 142 healthy, injury-free professional handball and ice hockey athletes of varying nationalities. In total, 145 athletes were screened. Three screened athletes were excluded from the study because of an elevated sBP at rest.

All athletes included were male Caucasians. All individuals were subjected to a physical examination, 12-lead electrocardiogram (ECG), and a progressive maximal cycling ergometer test. Age, height, weight, body mass index, history of professional training, and amount of training per week were determined. Body surface area was calculated using the formula of Du Bois.[25] Maximum workload, weight-adjusted workload, MET, heart rate at rest, brachial BP at rest, maximum heart rate, and maximum BP were assessed.

BP measurements

Resting brachial BP was measured before the exercise testing using a validated automatic device based on a standard sphygmomanometer technique (Boso clinicus, Bosch+ Sohn GmbH & Co KG, Germany). The cuff used for measurement was adjusted to the individual's arm circumference. Measurements were performed by a trained research associate on both arms in a sitting

position after a resting period of 5 min and repeated after 2 min. The average BP for each arm was calculated and the highest value was used for statistical analyses. Athletes with a resting sBP >140 mmHg or diastolic BP (dBP) >90 mmHg were excluded from the study.

Exercise testing and assessment of maximum BP

Athletes underwent a standardized progressive maximal cycling ergometer test with concurrent automatic brachial BP measurement and ECG recording (Schiller AG®, Switzerland). The exercise test protocol started with a load level of 100 W after a 2-min warm-up period that was conducted with 50 W. Loads were increased by 50 W every 2 min until exhaustion, which was defined as the participant's inability to maintain the load for 2 min. Next, the load was decreased to 25 W for 3 min of active recovery, followed by a 2-min cool-down period at rest. The test concluded with a final ECG recording and a brachial BP measurement. BP was measured once a minute during test and recovery periods, including at the maximum workload, immediately after the maximum workload, immediately after the end of the test, and after 5 min of recovery. Heart rate was measured with continuous ECG recording throughout the test and recovery periods. We assessed the absolute maximum workload of the athletes as well as the workload adjusted to individual body weight. Other measurements included maximum heart rate and heart rate at rest and 5 min after the exercise test.

Increases in sBP and dBP were calculated from peak and baseline (resting) values. Pulse pressure was calculated as sBP – dBP at rest and at maximum exercise. In addition, mean BP was determined as: dBP + (sBP – dBP)/3.

MET was estimated using standard equations of the ACSM for cycling ergometers.[22] The ΔsBP was calculated as (systolic maximum BP – sBP at rest) and indexed by the increase in METs from rest (ΔMETs calculated as peak MET – 1) to obtain the SBP/MET slope. Based on their SBP/MET slope, athletes were allocated to quartiles, as proposed and examined by Hedman et al.[3] Quartile I was defined as <4.3 mmHg/MET; quartile II as 4.3–6.2 mmHg/MET; quartile III as 6.2–9.0 mmHg/MET; and quartile IV as >9 mmHg/MET.

Statistical analysis

Descriptive analyses were carried out on all study variables for the total sample. Further, descriptive statistics were used on all study variables categorized by the SBP/MET slope. All data are presented as mean ± standard deviation. The Shapiro–Wilk test was used to confirm a normal distribution. In case of skewed distribution of the data, all analyses were performed on normalized data. Intergroup comparisons were made using analysis of variance and multiple linear regression models categorized by the SBP/MET slope, as described above. Bivariate relations were analysed using Pearson's product-moment correlation coefficient. Statistical significance was set at $p < 0.05$ (two-tailed) for all measurements. All statistical analyses were performed using the statistical software SPSS 25.0 for Mac (Statistical Package for the Social Sciences, Chicago, IL, USA).

Results

Cohort characteristics

A total of 142 professional handball and ice hockey athletes were included in the study. All participants were healthy and none took medication or supplementation. The clinical characteristics, anthropometric data, and specific training data of all athletes are displayed in Table 1. As expected, we found a significant correlation of age with history of professional training ($r = 0.965$, $p < 0.001$) and maximum heart rate ($r = 0.35$, $p < 0.01$). Further, body weight was weakly positively correlated with absolute workload ($r = 0.223$,

Table 1. Characteristics of all male 142 professional indoor athletes.

	Mean	SD
Age (y)	26.1	5.0
Height (cm)	189.6	6.7
Weight (kg)	92.9	10.3
Body mass index (kg/m^2)	25.8	1.9
Body surface area (m^2)	2.2	0.15
History of professional training (y)	10.37	4.9
Training per week (h)	17.95	3.1
Heart rate at rest (bpm)	55.8	9.4
Systolic BP (mmHg)	122.6	9.7
Diastolic BP (mmHg)	76.3	7.2
Pulse pressure at rest (mmHg)	46.3	10.5
Maximum heart rate (bpm)	177.9	10.3
Maximum systolic BP (mmHg)	197	20.3
Δ systolic BP (mmHg)	74.3	19.8
Δ diastolic BP (mmHg)	8.5	8.7
Maximum diastolic BP (mmHg)	84.9	7.8
Maximum pulse pressure (mmHg)	112.1	20.2
Absolute workload (Watt)	351.6	78.8
Relative workload (Watt/kg)	3.8	0.85
Peak energy expenditure (MET)	15.1	3.1
SBP/MET slope (mmHg/MET)	5.4	1.7

SD: standard deviation; BP: blood pressure; MET: metabolic equivalent of task; SBP/MET slope: increase in systolic BP per increase in MET.

$p = 0.008$), resting dBP ($r = 0.18$, $p = 0.025$), and height ($r = 0.795$, $p < 0.001$) and negatively correlated with MET ($r = –0.336$, $p < 0.001$). MET was negatively correlated with weight ($r = –0.264$, $p = 0.002$), height ($r = –0.176$, $p = 0.037$), body mass index ($r = –0.24$, $p = 0.04$), resting sBP ($r = –0.199$, $p = 0.018$), and resting dBP ($r = –0.169$, $p = 0.045$).

BP at rest

The mean resting BP was $123 \pm 10/76 \pm 7$ mmHg in all athletes. The highest measured resting sBP value was 139 mmHg and the highest measured dBP was 89 mmHg. None of the participants displayed a BP >140/90 mmHg. Resting sBP was positively correlated with maximum sBP ($r = 0.298$, $p < 0.001$), resting dBP ($r = 0.270$, $p = 0.001$), and maximum dBP ($r = 0.29$, $p = 0.12$). In addition, resting sBP was negatively associated with relative workload ($r = –0.170$, $p = 0.043$).

BPR to exercise

The mean maximum sBP/dBP in all athletes was $199 \pm 20/85 \pm 8$ mmHg, with a mean sBP increase of 74 ± 20 mmHg and a mean dBP increase of 8 ± 8 mmHg. The highest measured sBP was 253 mmHg and the highest dBP was 91 mmHg. The maximum pulse pressure was 112 ± 20 mmHg. Mean ΔsBP was 74.3 ± 20 mmHg and mean ΔdBP was 8.5 ± 9 mmHg (Table 1).

Maximum sBP was positively correlated with resting sBP ($r = 0.298$, $p < 0.001$) and maximum dBP ($r = 0.212$, $p = –0.01$). Further, we observed positive correlations with maximum pulse pressure ($r = 0.92$, $p < 0.001$), pulse pressure at rest ($r = 0.304$, $p < 0.001$), and SBP/MET slope ($r = 0.74$, $p < 0.001$).

Workload-indexed BPRs with SBP/MET slope calculation

All athletes completed the maximum exercise test until exhaustion and a maximum heart rate above the calculated individual 85% threshold (of individually calculated maximum heart rate). The mean maximum heart rate in all athletes was 178 ± 10 bpm and the mean absolute workload was 351 ± 79 W, with a corresponding relative workload of 3.8 ± 0.85 W/kg and MET of 15.1 ± 3.1. The mean workload-indexed BPR in the participants, calculated as SBP/MET slope, was 5.4 ± 1.7 mmHg/MET.

The cohort was divided into four groups according to SBP/MET slope quartile: I <4.3; II 4.3–6.2; III >6.2–9; and IV >9 mmHg/MET. As the highest SBP/MET slope calculated was 8.8 mmHg/MET, none of the athletes were assigned to the >9 mmHg/MET group. Forty-two athletes displayed a SBP/MET slope <4.2 mmHg/MET (I), 56 were assigned to the 4.3–6.2 mmHg/MET group (II), and 44 to the >6.2–9 mmHg/MET group (III). The mean SBP/MET slope values in these groups were 3.6 ± 0.6, 5.2 ± 0.5, and 7.6 ± 1 mmHg/MET, respectively.

There were no significant group differences in anthropometrics, history of professional training, heart rate at rest, BP at rest, maximum heart rate, and maximum dBP (see Table 2). In contrast, athletes in group III had a higher maximum sBP compared with the other groups ($p < 0.001$ for each) and those athletes with the lowest SBP/MET slope displayed the lowest maximum sBP (Figure 1). Further, the maximum pulse pressure was higher in the highest SBP/MET slope group III compared with the other groups ($p < 0.001$ for each). Significant differences between the groups were also found for ΔsBP ($p < 0.001$ for each comparison) and ΔdBP ($p = 0.011$ for comparison of I vs II and vs III; $p = 0.042$ for comparison of II vs III).

Athletes in group I achieved a higher absolute and relative workload compared with those in the other groups (Table 2; $p < 0.001$). In contrast, the achieved absolute ($p = 0.079$) and relative workload ($p = 0.081$) of groups II and III were not significantly different. The peak energy expenditure (MET) in athletes in group III with the highest SBP/MET slope (>6.2–9 mmHg) was significantly lower than in those in group II with 4.3–6.2 mmHg/MET ($p = 0.041$) and those in group I with the lowest SBP/MET slope ($p < 0.001$). Detailed data are given in Table 2.

Correlations of SPB/MET slope with performance and hemodynamic data

The SBP/MET slope was negatively correlated with absolute workload ($r = –0.463$, $p < 0.001$) as well as relative workload ($r = –0.499$, $p < 0.001$), whereas positive correlations were observed with maximum sBP ($r = 0.74$, $p < 0.001$), maximum dBP (0.204, $p = 0.015$), and maximum pulse pressure ($r = 0.662$, $p < 0.001$). Further, the ΔsBP ($r = 0.784$, $p < 0.001$) and the ΔdBP ($r = 246$, $p = 0.03$) correlated positively with the SBP/MET slope.

Linear regression analyses revealed that a higher ΔsBP ($p < 0.001$) is a statistically significant predictor of a higher SBP/MET slope ($r^2 = 0.616$, corrected $r^2 = 0.612$, $p < 0.001$, $F(1,140) = 223.7$, Durbin–Watson statistic 1.934). The regression result is shown in Figure 2. Thus, resting dBP, sBP, and maximum pulse pressure were not able to statistically significantly predict the SBP/MET slope.

Table 2. Main clinical characteristics and exercise test results of the study population according to the SBP/MET slope classification.

	<4.3 mmHg/MET	4.3–6.2 mmHg/MET	>6.2–9 mmHg/MET	*p*-value
Number of participants	42 (30%)	56 (39%)	44 (31%)	
Age (y)	26.6 ± 4.7	26.6 ± 5.3	25.1 ± 5	ns
Height (cm)	190.1 ± 5.8	188.6 ± 7.1	190.4 ± 7.1	ns
Weight (kg)	92.9 ± 9.3	91.9 ± 11	94.2 ± 10.4	ns
BMI (kg/m^2)	25.6 ± 1.4	25.7 ± 2	26 ± 2.2	ns
Body surface area (m^2)	2.2 ± 0.14	2.19 ± 0.16	2.2 ± 0.15	ns
Professional training (y)	10.5 ± 4.4	10.8 ± 5.3	9.7 ± 5	ns
Training per week (h)	18.4 ± 3.3	17.5 ± 3.2	18.2 ± 2.7	ns
Heart rate at rest (bpm)	55.3 ± 9	58 ± 9.8	53.6 ± 9	ns
Systolic BP (mmHg)	125.2 ± 10.4	120.6 ± 9.4	123 ± 9.5	ns
Diastolic BP (mmHg)	77.4 ± 7.6	76.6 ± 7.3	75.1 ± 6.7	ns
Pulse pressure at rest (mmHg)	47.8 ± 11.1	44 ± 9.6	47.8 ± 10.7	ns
Maximum heart rate (bpm)	176.9 ± 9.5	177.6 ± 10	179.1 ± 11.4	ns
Maximum systolic BP (mmHg)	180.1 ± 13.42***	195.1 ± 14.9*	215.6 ± 16.1	<0.001
Maximum diastolic BP (mmHg)	82.6 ± 7.3	86.1 ± 8.7	85.7 ± 7.9	ns
Maximum pulse pressure (mmHg)	97.6 ± 13.6***	109 ± 16.6*	129.8 ± 16.4	<0.001
Δ systolic BP (mmHg)	55 ± 13***	74.5 ± 14*	92.6 ± 12.2	<0.001
Δ diastolic BP (mmHg)	5 ± 6*	9.5 ± 8.6	10.6 ± 10	<0.05
Absolute workload (W)	392.2 ± 47.1***	352.2 ± 56.6	311.9 ± 45.6	<0.05
Relative workload (W/kg)	4.2 ± 1***	3.9 ± 0.7	3.3 ± 0.5	<0.05
Peak energy expenditure (MET)	16.7 ± 4***	15.4 ± 2.6	13.4 ± 1.7	<0.05
SBP/MET slope (mmHg/MET)	3.6 ± 0.6***	5.2 ± 0.5*	7.6 ± 1	<0.001

BMI: body mass index; BP: blood pressure; MET: metabolic equivalent of task; SBP/MET slope: increase in systolic BP per increase in MET.
*$p < 0.001$ vs >6.2–9 mmHg/MET.
**$p < 0.001$ vs 4.36.2 mmHg/MET.

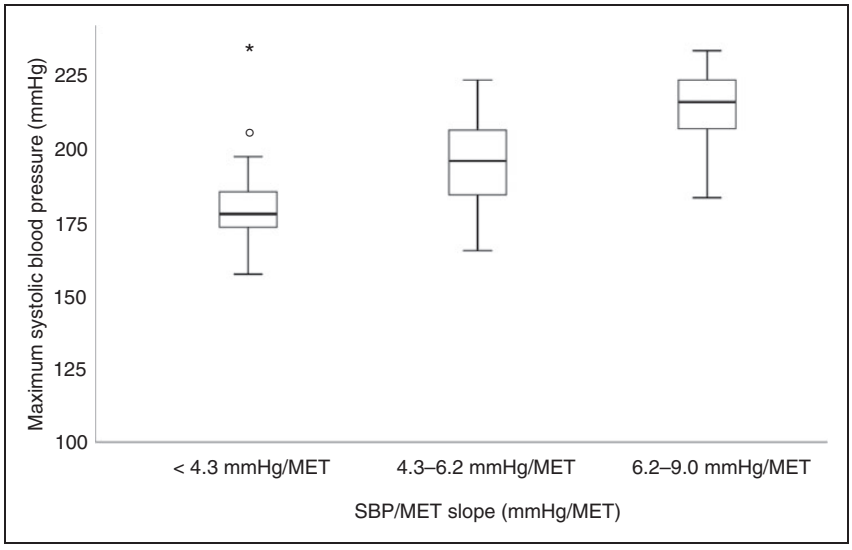

Figure 1. Maximum systolic blood pressure according to SBP/MET slope.

Discussion

To the best of our knowledge, our study is the first to investigate the BPR to a standardized maximum exercise test in healthy male professional indoor athletes and its correlation with the SBP/MET slope. Our main findings are that athletes with the lowest SBP/MET slope displayed the lowest maximum sBP and the lowest ΔsBP but achieved the highest absolute and relative workload. Further, the energy expenditure (MET) was higher in these athletes.

These findings were surprising, since we hypothesized that athletes with a higher maximum sBP would

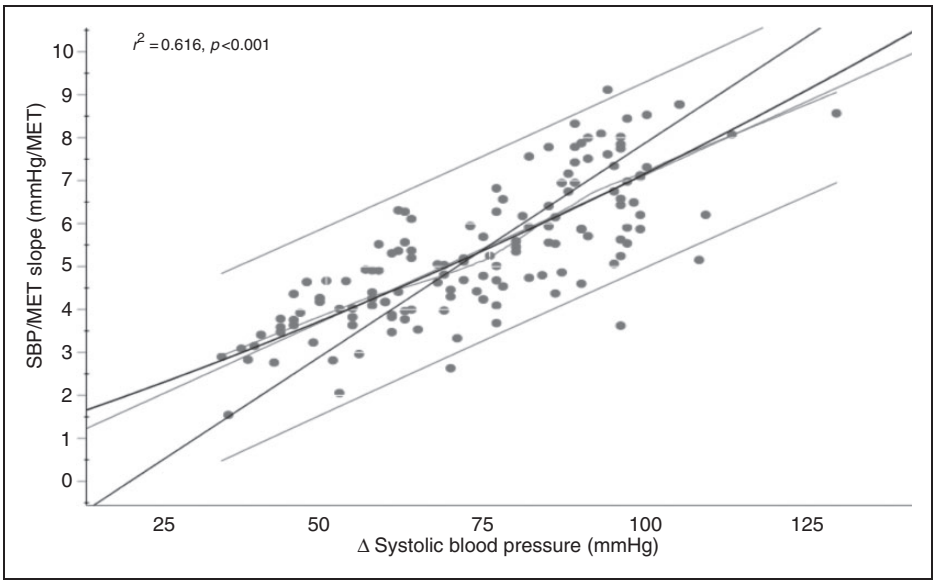

Figure 2. SBP/MET slope as a function of Δ systolic blood pressure.

have a better performance level than those with lower maximum sBP, assuming a linear relationship between sBP and external workload[16] and, consequently, an association of the highest sBP with the highest workload. Thus, contrary to our hypothesis, the current study showed that athletes with the least sBP increase and the lowest maximum sBP achieved the highest absolute and relative workload, indicating a better performance. These results are not consistent with the previously published data of Hedman et al.,[3] who found that individuals with a peak sBP <210 mmHg had a 20% higher relative risk of mortality. However, in this study, the mean age was 58 years and the participants were non-athletes with several cardiovascular risk factors, which limits comparison to our results.

In general, given the conflicting definitions of an exaggerated BPR,[4,13,14] a comparison across studies is challenging. Further, different exercise testing methods, BP measurement methods,[12,26] and determinations of sBP at submaximal[12] workload or maximum workload[26] limit meaningful comparisons. Therefore, to enable comparison to other studies, a detailed description of the exercise testing modalities is recommended.[13,27] In trained individuals, cycling ergometry has been shown to elicit higher maximum sBP compared to treadmill testing,[28] which was explained with the addition of isometric work (hand gripping) and elevated quadriceps muscle activity.[13] Thus, the determined maximum sBP of our study might be higher compared to treadmill testing.

Another important factor to consider when reviewing recent literature is the baseline risk factor profile and sex, especially in an athletic population, as the BPR to exercise is more pronounced in males than in females.[17] Thus, an exaggerated BPR to exercise was associated to a heightened risk for sudden cardiac death in men without a history of cardiovascular disease[5] and may contribute to autonomic imbalance and endothelial dysfunction, even in otherwise healthy individuals.

Data concerning the BPR to exercise in athletes are sparse, despite the fact that exercise testing plays a pivotal role in sports cardiology and is regularly performed as part of pre-participation screening.[29] Further, upper reference values are not defined, although Caselli et al.[18] proposed a threshold of 220 mmHg for male athletes. These same authors[16] reported a higher risk of developing arterial hypertension in male athletes with maximum sBP of 208 ± 22 mmHg. Interestingly, the normal BPR was determined to be 185 ± 20 mmHg, which is comparable to our own results in the group with the highest workload (180 ± 13 mmHg). The reported resting BP[18] was lower than in our study (116 ± 10/74 ± 7 vs 123 ± 10/76 ± 7 mmHg). Athletes performing "mixed exercise" demonstrated the highest resting BP,[18] which is in line with other publications.[17,30,31] Further, male athletes displayed a higher resting BP than females, as reported previously.[17,30,31] Our cohort can also be considered "mixed exercise" athletes. Unfortunately, the data presented by Caselli et al.[18] for mixed sports are not stratified by sex, which limits comparison. Further, the maximum workload in this study[18] was significantly lower compared with that of our group (268 ± 53 vs 349 ± 85 W) and, in addition, the maximum heart rate was significantly lower (166 ± 10 vs 178 ± 10 bpm).

This surprisingly low maximum heart rate (mean 25 ± 6 years) raises the question whether the exercise test carried out can be really considered to be a maximum exercise test. Lack of assessment of a workload-indexed BPR precludes correlation with SBP/MET slope status and thus also limits comparison with our results.

The maximum sBP of our professional indoor athletes (197 ± 20 mmHg) was lower than that reported by Pressler et al.,[17] who found a mean maximum BP of 204 ± 22 mmHg in their male professional athletes. Accordingly, the mean increase from resting sBP was lower in our cohort than in theirs (74 ± 20 vs 80 ± 20 mmHg). The study of Pressler at el. seems to be the most appropriate study to compare with ours, since their male cohort was of similar age and displayed a similar maximum heart rate (178 ± 10 vs 186 ± 12 bpm) and a comparable maximum power output (3.8 ± 0.85 vs 4.15 ± 0.61 W/kg). In addition, resting heart rate (56 ± 9 vs 60 ± 11 bpm) and resting sBP/dBP ($123 \pm 10/76 \pm 7$ vs $124 \pm 12/77 \pm 7$ mmHg) were comparable in the two study populations. However, as with the study by Caselli et al.,[18] the lack of a workload-adjusted BPR assessment by Pressler et al.[17] limits the comparison with our own results.

In fact, a workload-indexed characterization of BPR in elite athletes is not currently available in the literature. This is surprising, given the acknowledged difficulties in determining an exaggerated BPR in these populations, as a higher maximum sBP is linked to a better performance level. The ACSM recommendations[22] propose a normal increase in sBP per MET of 10 mmHg. However, in our cohort, the median SBP/MET slope was 5.4 mmHg/MET with a maximum SBP/MET slope of 8.7 mmHg/MET. In other observations, a median of 6.4 mmHg/MET[3] was observed, indicating that the proposed threshold of a 10 mmHg[22] increase in sBP/MET represent an upper limit rather than an average normal increase. Considering the recently published study of Hedman et al.[3] in which a higher SBP/MET slope was associated with worse survival, the proposed SBP/MET slope might be a useful tool to identify individuals at risk.

In our study, we identified a highly significant correlation between a lower SBP/MET slope and a higher accomplished workload and MET. This was consistent with the lower maximum sBP in athletes with a higher performance level compared with those with a higher maximum sBP and a lower performance level. Athletes in the lowest SBP/MET slope quartile (<4.3 mmHg/MET) displayed a higher MET despite a lower sBP. At first glance, these findings are surprising given the physiological increase in sBP with higher workloads. Yet, in hypertensive male elite athletes (sBP >130 mmHg according to American guidelines) a lower exercise capacity was found than in those with normal BP.[32] Under maximum exercise conditions, the maximum sBP in hypertensive athletes was 196 ± 18 mmHg compared with 182 ± 18 mmHg in athletes with a normal BP at rest.[32] These findings are in line with our own results, although our cohort was older (26 vs 23 years) and, consequently, displayed a lower maximum heart rate.

In summary, athletes with the lowest BPR displayed the highest exercise capacity, the highest workload, and a lower maximum heart rate than those with a higher BP.[32] This result might be explained by the excellent fitness of the professional athletes and the enhanced vascular function. The vascular function influences the maximum workload of male athletes[33] and contributes to higher performance and concomitantly lower BP, which is often not acknowledged in studies. The complex and ambiguous association between the BPR to exercise and sBP – with some studies indicating a lower cardiovascular risk with a lower maximum sBP[4] and other studies suggesting exactly the opposite[3,6] – might be explained by the often-neglected factors vascular function and vascular adaptation to exercise.[34]

Our findings emphasize the link between vascular function, BP, BPR, and physical performance in athletes. Today, the ability to examine vascular function and central haemodynamic parameters including central BP (cBP) via non-invasive tools might offer additional new opportunities to define workload-adjusted thresholds of a normal BPR to exercise in an athletic population.[35] Therefore, further studies that investigate the impact of vascular function and cBP on the BPR to exercise in athletes are needed to identify athletes at risk of developing hypertension.

Limitations

Our study has a few limitations. The number of participants limited its power to reveal potential correlations between SBP/MET slope status and markers of cardiac and vascular function other than brachial BP and the BPR to a maximum exercise test. The focus on professional indoor handball and ice hockey players may limit extrapolation of the results to other sport disciplines; however, as these team sports expose athletes to the haemodynamic stress of frequent interval sprints, they are representative of other sports with a high dynamic component (>75% VO_2max) and a moderate static component (10–20%).[23] A further limitation is our exclusive focus on male athletes, which precludes the extrapolation of our results to female athletes. We are currently addressing all three issues by extending our research to include larger numbers of professional male and female athletes from various sport disciplines.

Conclusions

Athletes are more frequently exposed to exercise-induced high BP than sedentary individuals, and exercise testing is frequently performed in the cardiovascular evaluation of competitive athletes.[31] Therefore, reliable cut-off values have to be established and, given the workload-dependent BPR to exercise, a workload-adjusted approach instead of using absolute cut-off values might be a good strategy for identifying athletes with an exaggerated BPR.[3]

In our cohort, the ΔsBP was predictive of an increase in SBP/MET slope and might be an additional tool to identify athletes at risk of developing hypertension. Our athletes with the lowest SBP/MET slope displayed the lowest BPR but the best performance level. Therefore, the SBP/MET slope might help to identify athletes with an exaggerated BPR, which constitutes a major risk of developing arterial hypertension in the future. Further, a higher SBP/MET slope was associated with a lower physical performance level, which compromises athletic performance.

Author contribution

PB, AM, CH, OD, and HN contributed to the conception and design of the study. PB, AM, and LK contributed to the acquisition, analysis, or interpretation of data for the work. PB and AM drafted the manuscript. PB, AM, LK, CH, OD, and HN critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of conflicting interests

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Blood Pressure Response and Vascular Function of Professional Athletes and Controls

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ABSTRACT

Workload-indexed blood pressure response (wiBPR) to exercise has been shown to be superior to peak systolic blood pressure (SBP) in predicting mortality in healthy men. Thus far, however, markers of wiBPR have not been evaluated for athletes and the association with vascular function is unclear. We examined 95 male professional athletes (26 ± 5 y) and 30 male controls (26 ± 4 y). We assessed vascular functional parameters at rest and wiBPR with a graded bicycle ergometer test and compared values for athletes with those of controls. Athletes had a lower pulse wave velocity (6.4 ± 0.9 vs. 7.2 ± 1.5 m/s, p = 0.001) compared to controls. SBP/Watt slope (0.34 ± 0.13 vs. 0.44 ± 0.12 mmHg/W), SBP/MET slope (6.2 ± 1.8 vs. 7.85 ± 1.8 mmHg/MET) and peak SBP/Watt ratio (0.61 ± 0.12 vs. 0.95 ± 0.17 mmHg/W) were lower in athletes than in controls (p < 0.001). The SBP/Watt and SBP/MET slope in athletes were comparable to the reference values, whereas the peak SBP/Watt-ratio was lower. All vascular functional parameters measured were not significantly correlated to the wiBPR in either athletes or controls. In conclusion, our findings indicate the potential use of the SBP/Watt and SBP/MET slope in pre-participation screening of athletes. Further, vascular functional parameters, measured at rest, were unrelated to the wiBPR in athletes and controls.

Introduction

Blood pressure response (BPR) to exercise testing has been recognized for its potential to uncover otherwise undetectable cardiovascular (CV) pathology and future CV risk in two different settings: routine clinical investigations of the general population [1, 2], and in pre-participation screenings of athletes [3–5]. Hence, knowledge

of what constitutes a normal or abnormal blood pressure response (BPR) to exercise is a crucial component of the cardiovascular evaluation.

Though, studies investigating the BPR to exercise delivered inconsistent results with some studies indicating a lower cardiovascular risk with a lower maximum systolic blood pressure (SBP) [2] and other studies suggesting exactly the opposite [6, 7]. In conclusion, the clinical impact of blood pressure response (BPR) during exercise still remains a controversial issue [8–10], and the European Society of Cardiology states in its latest guideline that there is currently no consensus on normal BPR during exercise [11].

Therefore a call to re-evaluate guidelines for BPR to exercise has recently been made, intended to stimulate research into establishing more reliable markers of BPR [12]. At the same time, novel markers of vascular function have emerged whose feasibility for acquisition at rest via noninvasive oscillometric devices could simplify clinical assessment in uncovering functional impairment [13, 14]. Functional vascular impairment might lead to an exaggerated BPR to exercise even in the absence of hypertension at rest [15, 16]. Further, arterial stiffness predicted an exaggerated BPR in young individuals [17], indicating that vascular functional assessment might provide additional information for cardiovascular risk classification.

Acknowledging these discoveries, Hedman et al. investigated a workload-indexed BPR (wiBPR), expressed as the slope of systolic blood pressure in response to workload (SBP/MET slope) [6], and demonstrated that currently proposed thresholds for BPR to exercise did not align well with observations in their middle-aged population. The 10 mmHg/MET benchmark that has been discussed to constitute a normal increase [18] was far in excess of the 5 mmHg/MET and 10 mmHg/MET observed by Hedman et al. [6] to represent the 50th and 95th percentile in their study's low-risk sub-population. Moreover, a SBP/MET slope > 6.2 mmHg/MET was associated with a 27 % higher risk of mortality over 20 years in males compared with those with a SBP/MET slope < 4.3 mmHg/MET [6].

These findings underscore that current threshold recommendations for BPR to exercise lack clinical utility. Further, these observations highlight the need for the development of normative values of wiBPR for athletes' pre-participation evaluation. We have shown that male athletes present with a mean SBP/MET slope of 5.4 mmHg/MET and that those with the lowest SBP/MET slope also displayed the lowest maximum SBP and the highest performance level [19]. Consistent with these results, we recently demonstrated that the resistance index, as a direct physical marker of global vascular resistance, was able to predict maximum power output in elite athletes [20].

Therefore, we now investigated vascular function and the newly introduced markers of wiBPR, specifically SBP/W slope and peak SBP/W ratio [21] in a cohort of professional male athletes and male controls. The peak SBP/W ratio represents the ratio of peak SBP to maximum achieved watts (W) in response to bicycle ergometer, whereas the SBP/W slope reflects the increase of SBP per W increment and thus the steepness of SBP in relation to workload, with higher values representing a steeper increase [21].

We hypothesized that athletes would display an enhanced vascular function compared to controls with measureable differences at rest. Further, we anticipated finding a lower wiBPR in athletes compared to controls and to recently published normative values [21] as a result of this enhanced vascular function. In addition, we expected to find significant correlations of vascular functional parameters with the wiBPR in athletes and controls.

Materials and Methods

Study design

The study was conducted as a cross-sectional, single-center pilot study as part of the routine pre-season medical monitoring program of the first German handball division. Data were collected in the second half of July in the years 2017–2019 after a six-week competition-free interval. Competitive team handball is classified as high-intensity mixed sports with a high load for the cardiovascular system. It is characterized by requiring the repetition of high-intensity activities with brief recovery periods. Players need the ability to perform repeated maximal or near-maximal intensities such as sprinting, jumping, and changing of directions throughout the match.

Age-matched male controls were recruited as volunteers and included in the study when they participated in sports activities < 1 hour per week.

All participants received a clear explanation of the study and provided their written informed consent. Further, they filled out a questionnaire regarding health status, medication, nutrition supplementation, amount of training, and history of training (pre-participation questionnaire of the European Federation of Sports Medicine Associations). Only healthy individuals free of underlying cardiovascular diseases, risk factors, and medication were included. The local ethics committee approved the study protocol. The study was performed in accordance with the ethical standards in sport and exercise science research [22].

Study population

The participants were 95 healthy male professional handball players of the first German division and 30 healthy male controls. All participants included were Caucasians, non-smokers, and none took medication or multivitamin supplements. Age, height, weight, and body mass index were determined. Body surface area was calculated using the formula of DuBois and DuBois [23].

Exercise testing and assessment of blood pressure, heart rate and performance

All individuals were subjected to a physical examination and 12-lead electrocardiogram (ECG). Further, all participants underwent a standardized progressive maximal cycling ergometer test with concurrent automatic brachial BP measurement (Schiller AG, Baar, Switzerland) and 12-lead ECG recording. The cuff used for measurement was adjusted to the individual's arm circumference. The first BP measurement was performed on the right arm in a sitting position on the ergometer after a resting period of 5 min (resting BP). The participants were instructed to let their right arm hang loosely during BP measurements, when possible. The exercise test protocol of the athletes started with a load level of 100 W after a 2-min warm-up period that was conducted with 50 W. Controls started with 50 W after a warm-up period conducted with 25 W.

Loads were increased by 50 W in athletes and 25 W in controls every 2 min until exhaustion, which was defined as the participant's inability to maintain the load for 2 min. If participants could not complete the last 2-min stage, the individual maximum workload was calculated depending on the percentage duration of the last stage. Further, the rating of perceived exertion (RPE, Borg) was evaluated every 2 minutes, but not used as a termination criterion. Next, the load was decreased to 25 W for 2 min of active recovery that was followed by a 3-min cool-down period at rest. The test concluded with a final ECG recording and brachial BP measurement. BP was measured at every stage during test and recovery periods, including at the maximum workload. Each BP measurement was recorded automatically with the corresponding time, heart rate, and workload. The calculated maximum heart rate was determined with the formula validated for cycling ergometries ((208–(age * 0.7)). However, the predicted maximum heart rate was not used as a termination criterion.

Increases in systolic and diastolic BP were calculated from peak and baseline (resting) values. Pulse pressure was calculated as SBP–DBP at rest and during exercise. In addition, mean BP was determined as: DBP + (SBP–DBP)/3. MET values were estimated using the following formula validated for cycling ergometers: MET = (((Watt * 1.8 * 6.12)/kg)) + 7)/3.5 [18]. The ΔSBP was calculated as (maximum SBP–resting SBP) and was indexed by the increase in MET from rest (ΔMET calculated as peak MET–1) to obtain the SBP/MET slope [6]. The peak SBP/W ratio was determined as peak SBP/peak workload in W [21]. The SBP/W slope was calculated as the ratio of the difference in SBP from the first to the last BP measurement during exercise over the difference in workload in W between these two measures (last SBP–first SBP)/(last W–first W) [21].

Non-invasive assessment of peripheral and central blood pressure and pulse pressure waveforms

We used the non-invasive vascassist2 device (isymed GmbH, Butzbach, Germany) to acquire pulse pressure waveforms by means of oscillometry. The device uses a validated model [14, 24] of the arterial tree, which replicates an individual's acquired pulse pressure waves. The vascular evaluation was carried out before exercise testing in a room with a comfortable and stable temperature of 22 °C and a lack of external stress influences. After a 15-min rest period, measurements were performed in a supine position using four conventional cuffs adapted to the upper arm and forearm circumferences of the participants. Both radial and brachial pulse pressure waves were acquired simultaneously on both arms with step-by-step deflation of the cuffs and analyzed. Brachial and radial BP, central blood pressure (CBP), aortic pulse wave velocity (PWV), augmentation index at a heart rate of 75 bpm (Aix@75), resistance index (R), total vascular resistance, stroke volume, cardiac output, and ejection duration were calculated.

Statistical analysis

Descriptive analyses were carried out on all study variables for the total sample and separated by athletes and controls. All data are presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to determine normal distribution. Between-group comparisons were made using independent sample t tests. Bivariate relations were analyzed using the Spearman correlation coefficient. Pearson's product-moment correlation coefficient was used to determine linear correlations between vascular functional parameters and exercise test results. Statistical significance was set at $p < 0.05$ (two-tailed) for all measurements. Relationships between wiBPR and vascular functional parameters were explored using bivariate correlation and multiple linear regression analysis. All statistical analyses were performed using the SPSS statistical software (IBM SPSS Statistics for Macintosh, Version 25.0; IBM Corp., Armonk, NY, USA).

Results

Cohort characteristics

A total of 125 male participants, 95 athletes and 30 healthy, age-matched controls, were included in the study. Athletes were taller and heavier and displayed a greater body surface area than controls (▶ **Table 1**); however, age ($p = 0.292$) and body mass index were not different between groups ($p = 0.206$). The mean resting heart rate was lower in athletes than in controls (57 ± 10 vs. 70 ± 14 bpm, $p < 0.001$). Further clinical characteristics, anthropometric data, and specific training data are displayed in ▶ **Table 1**. As expected, we found a significant correlation of age with history of professional training ($r = 0.956$, $p < 0.001$) in athletes.

Blood pressure and vascular function at rest

The mean resting brachial SBP and the mean brachial BP was lower in athletes than in controls. None of the participants displayed a BP > 140/90 mmHg. Athletes had a significantly lower diastolic CBP, mean CBP and PWV compared with controls, whereas systolic CBP, Aix@75, resistance index (R), and total vascular resistance were not different between the groups. In contrast, the central pulse pressure was higher in athletes than in controls. Detailed data are presented in ▶ **Table 2**.

Heart rate and blood pressure response to exercise

The test duration between athletes and controls was not different (1060 ± 100 vs. 1005 ± 150 sec, $p = 0.102$). All participants achieved a maximum heart rate above the threshold of 85 % of the individual calculated maximum heart rate with significant differences between the two groups (athletes 94.4 ± 5.1 % vs. controls 98.6 ± 4.7 %, $p < 0.001$). In consequence, maximum heart rate during the exhaustive exercise test was significantly lower in athletes than in controls (179.4 ± 9.8 vs. 187.1 ± 9.9 bpm, $p < 0.001$). However, the rating of

▶ **Table 1** Clinical characteristics of athletes (n = 95) and controls (n = 30)

	Athletes n = 95		Controls n = 30		p value
	Mean	SD	Mean	SD	
Age (years)	25.6	5	26.2	4.4	0.292
Height (cm)	188.5	7.2	183.8	6.2	0.002
Weight (kg)	91.5	10.7	85.1	8.3	0.003
Body mass index (kg/m²)	25.7	2	25.17	1.9	0.206
Body surface area (m²)	2.18	0.16	2.08	0.12	0.001
Training history (years)	9.85	4.95	0.03	0.18	< 0.001
Training per week (hours)	17.45	3.1	0.5	0.2	< 0.001

▶ **Table 2** ▶ **Results of vascular evaluation in athletes (n = 95) and controls (n = 30)**

	Athletes n = 95		Controls n = 30		p value
	Mean	SD	Mean	SD	
Brachial systolic BP (mmHg)	123	10.2	129	11.5	0.013
Brachial diastolic BP (mmHg)	76	7	78	8.5	0.196
Mean brachial BP (mmHg)	91.8	6.8	95.1	8	0.053
Pulse pressure at rest (mmHg)	46.8	10	50.4	11.3	0.098
Heart rate at rest (bpm)	57.2	10.3	70.1	13.6	< 0.001
Mean aortic blood pressure (mmHg)	76	10	82	9.8	0.005
Central systolic BP (mmHg)	99	8	102	9.3	0.052
Central diastolic BP (mmHg)	63	9.7	69	9.3	0.003
Central pulse pressure (mmHg)	38	6.6	34	6.4	0.019
Aortic pulse wave velocity (m/s)	6.4	0.92	7.2	1.5	0.001
Augmentation index @75 bpm (%)	−18.6	10	−16	10	0.38
Resistance index	16.4	6.3	17.7	7.4	0.346
Total vascular resistance (dyn * sec/cm^5)	1336	298	1267	333	0.294

perceived exertion was not different between the groups (18.5 ± 1.1 vs. 19.2 ± 0.9 Borg scale, p = 0.065).

The heart rate, SBP, DBP, mean brachial BP, and pulse pressure were significantly lower in athletes compared to controls (< 0.001) at 100, 150 and 200 W workload. All controls completed the 150 W stage, 22 (66 %) accomplished the 200 W stage, 8 (26 %) the 250 W stage, and 1 (3 %) achieved the 300 W stage. All athletes (95) completed the 250 W stage, 86 (82 %) the 300 W stage, 48 (46 %) the 350 W stage, 21 (20 %) the 400 W stage, and 5 athletes (5 %) accomplished more than the 450 W stage, respectively.

Despite the differences throughout the stages of the graded exercise test, the maximum SBP (200 ± 20 vs. 197 ± 19 mmHg, p = 0.358), maximum DBP (84.7 ± 7.1 vs. 86.4 ± 10.1 mmHg, p = 0.391), mean brachial BP (123.5 ± 9 vs. 123.3 ± 11.6 mmHg, p = 0.893) and maximum pulse pressure (115.4 ± 19.8 vs. 110.6 ± 13.6 mmHg, p = 0.211) were not different between athletes and controls at the individual peak exercise. ΔSBP and Δpulse pressure were higher in athletes, but ΔDBP and Δmean brachial BP were not different between groups. The complete data set is presented in ▶ **Table 3**. In addition, the blood pressure responses at each stage are depicted in ▶ **Figure 1**. Further, ▶ **Figure 2** shows the SBP according to the achieved maximum workload.

Maximum SBP was positively correlated with resting SBP (r = 0.241, p = 0.019) and maximum DBP (r = 0.234, p = –0.022). In addition, resting SBP was negatively associated with R (r = –0.289, p = 0.005).

Workload-indexed blood pressure responses

Athletes achieved a significantly higher absolute workload than controls with a correspondingly higher relative workload and MET. All markers of a workload-adjusted BPR were significantly lower in athletes than in controls: SBP/MET slope (6.2 ± 1.8 vs. 7.85 ± 1.8 mmHg/MET, p < 0.001); SBP/W slope (0.35 ± 0.13 vs. 0.44 ± 0.12 mmHg/W, p < 0.001) and the peak SBP/W ratio (0.61 ± 0.12 vs. 0.95 ± 0.17 mmHg/W, p < 0.001) (▶ **Table 3**). The respective percentiles for the BP increase and the wiBPR for athletes are displayed in ▶ **Table 4**.

All vascular functional parameters, measured at rest, were not significantly correlated to SBP/MET slope, the peak SBP/W ratio, or the SBP/W slope in either athletes or controls.

Regression analyses of the influence of the hemodynamic data of athletes and controls on different markers of workload-indexed blood pressure response

We performed multivariate regression analyses to explore possible linear associations across the vascular functional parameters measured at rest with the workload- indexed markers of BPR. We used brachial systolic BP, brachial diastolic BP, central systolic and diastolic BP, mean central BP, central pulse pressure, PWV, Aix@75 bpm, R and total vascular resistance as predictors of the regression model and, separately, the SBP/MET slope, the peak SBP/W ratio, and SBP/W slope as continuous dependent variables in both athletes and controls. All evaluated regression models were unable to predict the markers of workload- indexed BPR in both groups and neither of the evaluated vascular functional parameters at rest were found to be independent determinants of the workload-indexed BPR.

Discussion

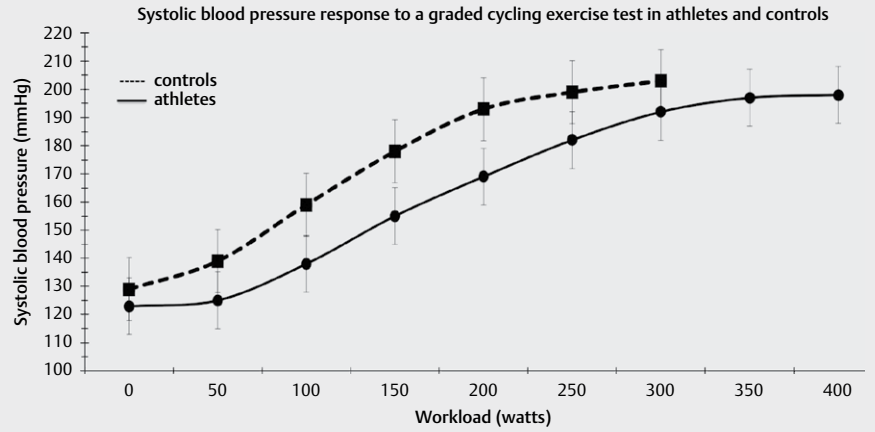
The present study represents the first analysis of vascular function and the newly introduced workload-adjusted markers of BPR, such as SBP/MET slope, SBP/W slope, and peak SBP/W ratio, to a maximum exercise test in professional athletes and sedentary controls.

Our main findings are that 1) athletes displayed a significantly lower wiBPR than did sedentary controls despite a higher achieved absolute and relative workload; 2) all markers of wiBPR were markedly lower in athletes, although the absolute values of maximum SBP were not different between athletes and controls; 3) further, despite a lower PWV and lower mean CBP at rest, all other vascular markers measured at rest, including total vascular resistance and resistance index, were not different between athletes and sedentary controls; 4) none of the measured markers of vascular function were able to predict the wiBPR in either athletes or controls; 5) in athletes, the SBP/Watt and the SBP/MET slope, but not the peak SBP/W ratio, were comparable to the recently published reference values for bicycle ergometers.

▶ **Table 3** ▶ Results of vascular evaluation and exercise testing in athletes (n = 95) and controls (n = 30).

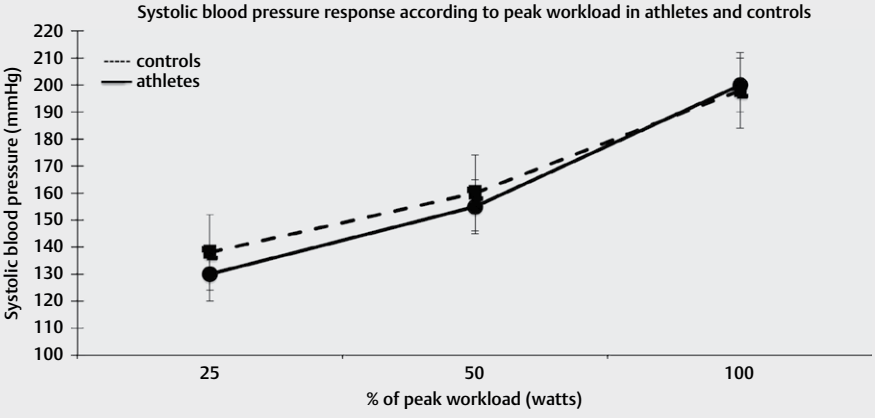
	Athletes n = 95		Controls n = 30		p value
	Mean	**SD**	**Mean**	**SD**	
Rest					
Brachial systolic BP (mmHg)	123	10.2	129	11.5	0.013
Brachial diastolic BP (mmHg)	76	7	78	8.5	0.196
Mean brachial BP (mmHg)	91.8	6.8	95.1	8	0.053
Pulse pressure at rest (mmHg)	46.8	9.9	50.4	11.3	0.098
Heart rate at rest (bpm)	57.2	10.3	70.1	13.6	<0.001
100 Watts					
Brachial systolic BP (mmHg)	138	14.1	159	17.6	<0.001
Brachial diastolic BP (mmHg)	76	7.3	80.8	7.7	0.005
Mean brachial BP (mmHg)	97.2	7.4	107.2	9.5	<0.001
Pulse pressure (mmHg)	62.6	14.6	79.1	14.7	<0.001
Heart rate (bpm)	105.2	11.8	129.4	16.5	<0.001
150 Watts					
Brachial systolic BP (mmHg)	155.4	15.6	178.4	17.5	<0.001
Brachial diastolic BP (mmHg)	77.5	8.7	83.4	7	<0.001
Mean brachial BP (mmHg)	103.5	9.3	115.1	9.1	<0.001
Pulse pressure (mmHg)	77.9	14.1	95	14.7	<0.001
Heart rate (bpm)	123.8	13.2	156.2	18.6	<0.001
200 Watts					
Participants	95 (100 %)		22 (66 %)		
Brachial systolic BP (mmHg)	168.7	17.9	193	19.3	<0.001
Brachial diastolic BP (mmHg)	80.6	11.6	88.3	9.3	<0.001
Mean brachial BP (mmHg)	110	10.8	122.3	10.8	<0.001
Pulse pressure (mmHg)	89.3	16.2	102.7	13.9	<0.001
Heart rate (bpm)	143.7	13.8	177.1	17.7	<0.001
250 Watts					
Participants	95 (100 %)		8 (26 %)		
Brachial systolic BP (mmHg)	181.6	18.8	195.1	12.4	0.012
Brachial diastolic BP (mmHg)	83.8	11.4	85.7	7.3	0.716
Mean brachial BP (mmHg)	116.4	12.8	123.5	14.1	0.024
Pulse pressure (mmHg)	97.1	14.3	112.8	12.1	0.001
Heart rate (bpm)	162.1	15.3	183.6	10.9	<0.001
Peak exercise					
Time (sec)	1060	100	1005	150	0.102
Rating of perceived exertion (Borg scale)	18.5	1.1	19.2	0.9	0.065
Maximum heart rate (bpm)	179.4	9.8	187.1	9.9	<0.001
Max. heart rate (% of calculated max. heart rate)	94.4	5.1	98.6	4.7	<0.001
Absolute workload (watts)	339.2	64	211	35.2	<0.001
Relative workload (watts/kg)	3.73	0.8	2.5	0.44	<0.001
Peak energy expenditure (MET)	13.9	2.5	9.9	1.4	<0.001
Maximum systolic brachial BP (mmHg)	200.4	20.1	197	18.1	0.358
Maximum diastolic brachial BP (mmHg)	84.7	7.1	86.4	10.1	0.391
Mean brachial BP (mmHg)	123.5	9	123.3	11.6	0.893
Maximum pulse pressure (mmHg)	115.4	19.8	110.6	13.6	0.211
Changes from baseline					
Δ systolic brachial BP (mmHg)	77	20	68	14	0.004
Δ diastolic brachial BP (mmHg)	8.8	9.3	7.5	6.5	0.395
Δ mean brachial BP (mmHg)	31.7	10.2	28.2	7.8	0.09
Δ pulse pressure (mmHg)	68.6	18.4	60.1	12.5	0.021
Workload- indexed blood pressure response					
SBP/MET slope (mmHg/MET)	6.20	1.8	7.85	1.8	<0.001
SBP/Watt slope (mmHg/Watt)	0.34	0.13	0.44	0.12	<0.001
Peak SBP/Watt- ratio (mmHg/Watt)	0.61	0.12	0.95	0.17	<0.001

The SBP/Watt-slope was calculated as: (increase in systolic blood pressure (SBP) from first to last SBP measure during exercise) / (the increase in workload (watts) between those two measures). The peak SBP/Watt ratio was calculated as: (SBP at peak measure during exercise / (the workload (watts) at last SBP). The SBP/MET slope was calculated as follows: (Peak SBP – first SBP)/ (peak MET – 1 MET). BP, blood pressure; MET, metabolic equivalent of task; SBP, systolic blood pressure; SD, standard deviation.



Athletes (n)	95	95	95	95	95	95	86	48	21
Controls (n)	30	30	30	30	22	8	1	0	0

▶ **Fig. 1** Systolic blood pressure response to a graded cycling exercise test in athletes and controls.



▶ **Fig. 2** Systolic blood pressure response according to peak workload in athletes and controls.

▶ **Table 4** Systolic blood pressure response to exercise in athletes (n = 95).

	Rest (mmHg)	100 W (mmHg)	150 W (mmHg)	200 W (mmHg)	250 W (mmHg)	SBP/MET slope (mmHg/MET)	SBP/W slope (mmHg/W)	Peak SBP/W-ratio
10th percentile	110	122	136	143	158	3.88	0.19	0.46
20th percentile	113	127	143	152	165	4.56	0.24	0.52
30th percentile	117	132	149	161	170	5.11	0.275	0.55
40th percentile	120	135	152	165	174	5.57	0.29	0.57
50th percentile	124	140	156	168	180	5.95	0.32	0.59
60th percentile	125	143	160	174	187	6.47	0.35	0.61
70th percentile	128	147	165	180	191	7.12	0.385	0.65
80th percentile	132	152	169	184	198	8.0	0.44	0.72
90th percentile	136	159	175	190	206	8.8	0.49	0.77

Our study provides the first comparison of the newly introduced markers of workload-indexed BPR to exercise in male professional athletes and age-matched controls.Recently, Hedman et al. [21] reported age- and sex-specific reference equations for workload-indexed systolic BPR during bicycle ergometry for the general population. The SBP/W slope, reflecting the increase of SBP per W increment and thus the steepness of SBP in relation to workload, was introduced and suggested to deliver additional data for risk classification.

The BPR to exercise in men is characterized by an increase in cardiac output and by an increase in total peripheral resistance [25] and therefore less influenced by fitness levels. Hence, the values of the SBP/W slope in our male athletes were comparable (0.34 ± 0.12 vs. 0.33 ± 0.11 mmHg/W) to the proposed reference values of the general population, whereas the SBP/W slope of our healthy control group (0.44 ± 0.12 mmHg/W) was markedly higher [21].

In contrast to the aforementioned, the absolute values of the peak SBP/W ratio in our cohort of professional athletes were lower compared to the published reference values [21] (0.61 ± 0.12 vs. 0.73 ± 0.11 mmHg/W), whereas the control group exceeded the normative 95th percentile (0.95 ± 0.17 mmHg/W) [21]. Given that our athletes had significantly greater cardiorespiratory fitness (CRF) than the participants of the Hedman study, it is tempting to speculate that CRF affects the peak SBP/W ratio. Hence, the peak SBP/W ratio of athletes might be lower compared to that of controls, as athletes usually achieve higher workloads. In consequence, these results raise the question whether athletes might need different thresholds for the peak SBP/Watt ratio.

The ACSM recommendations [18] propose a normative SBP/MET slope of 10 mmHg/MET. However, in our cohort, the mean SBP/MET slope was 6.2 mmHg/MET for athletes and 7.85 mmHg/MET for controls. In other observations a median of 6.4 mmHg/MET in a normal population [6] and 5.4 mmHg/MET in an athletic population [19] were reported. Of note and in line with the aforementioned, the 95th percentile of the SBP/MET slope in our examined athletes was 9.42 mmHg/MET and 10.3 mmHg/MET in our control group, respectively [18]. In conclusion, our findings clearly indicate that the ACSM threshold of 10 mmHg/MET [18] represents an upper limit and not an average normal increase.

The healthy, but sedentary control group of our study exceeded the normative values of all measured markers of wiBPR, which suggests an increased cardiovascular risk. Therefore, preventive interventions to avoid the development of arterial hypertension and cardiovascular disease should be established in this group.

Taken together, our data emphasize the need to use wiBPR instead of absolute values, as the maximum SBP was not different between athletes and controls. Reliable and validated reference values for athletes should be established to define an exaggerated BPR in these cohorts in order to identify athletes at risk of developing arterial hypertension.

So far, our studies delivered reference values for the SBP/MET slope in an athletic population of > 200 professional male athletes in total [19]. These results are in line with the proposed normative values that were derived from 285 healthy males in this age cohort [21]. To this end, the aforementioned data concerning the SBP/MET slope are promising [6].

Hedman et al. [21] and others [26] hypothesized that total peripheral vascular resistance contributes to BPR and physical performance. Hence, our previous study [20] revealed the impact of the resistance index (R) on physical performance in athletes. However, in the current study, neither R nor global vascular resistance at rest was different between athletes and controls, and consequently they were not able to predict the wiBPR in athletes. Moreover, measuring of PWV was proposed to provide additional information for cardiovascular risk classification as it predicted an exaggerated BPR in normotensive individuals [17]. The PWV of 6.4 m/s measured in our athletes is in line with other studies [20, 27] and meta-analyses [28]. Athletes performing predominantly aerobic exercise are likely to display a lower PWV than sedentary individuals [28, 29], represented by our control group. Further, aerobic exercise training was shown to reverse age-related aortic stiffness [30]. Thus, in our study, all vascular functional parameters were not able to predict the wiBPR in both groups. The difference of our findings to the aforementioned study [17] might be explained with our investigated study cohort of professional athletes, who displayed a low PWV. Further, Haarala et al. [17] did not present their data separately for males and females, which limits comparison to our own results.

Hence, it may be speculated that resistance index and global vascular resistance differ during exercise conditions and lead to the detected difference in the wiBPR with athletes displaying a higher arterial vasodilator reserve. Unfortunately, vascular resistance could not be measured during exercise to substantiate this hypothesis. Taken together, these results highlight the problems inherent with the use of non-invasive devices that evaluate vascular function via oscillometry [13]. These validated methods deliver reliable results at rest, but owing to the measurement technique, not during an exhaustive exercise test [13].

As total vascular resistance at rest and maximum SBP were not different between athletes and controls, our data indicate the importance of vascular function and total vascular resistance during exercise for the BPR to exercise.

Limitations and strengths

Our study has a few limitations. The number of participants limited its power to uncover potential correlations between the wiBPR parameters measured and markers of cardiac and vascular function other than CBP, PWV, total vascular resistance, and brachial BP. In addition, the number of included athletes precludes the determination of reference values. The focus on professional male handball players limits extrapolation of the results to other sport disciplines and to female athletes. Further, the different ramp grading of the exercise testing between athletes and controls may have affected our results.

However, we did include a homogeneous cohort of experienced elite athletes and controls of the same age without cardiovascular disease and free of medication. Further, the rigid design of measuring vascular function and accomplishing an exhaustive and standardized exercise test in both groups must be mentioned, which strengthens our analysis.

Conclusions

In conclusion, our findings may aid clinicians and exercise physiologists in interpreting the BPR to exercise and provide a basis for future research on the prognostic impact of exercise BPR. Especially the SBP/MET slope might already be used in male athletes to de-

termine wiBPR to exercise [6, 19]. Vascular functional parameters were not correlated to the wiBPR in either athletes or controls despite their potential to detect occult cardiovascular impairment.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Sex differences in workload-indexed blood pressure response and vascular function among professional athletes and their utility for clinical exercise testing

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Abstract

Purpose Sex differences in blood pressure (BP) regulation at rest have been attributed to differences in vascular function. Further, arterial stiffness predicts an exaggerated blood pressure response to exercise (BPR) in healthy young adults. However, the relationship of vascular function to the workload-indexed BPR and potential sex differences in athletes are unknown.

Methods We examined 47 male (21.6 ± 1.7 years) and 25 female (21.1 ± 2 years) athletes in this single-center pilot study. We assessed vascular function at rest, including systolic blood pressure (SBP). Further, we determined the SBP/W slope, the SBP/MET slope, and the SBP/W ratio at peak exercise during cycling ergometry.

Results Male athletes had a lower central diastolic blood pressure (57 ± 9.5 vs. 67 ± 9.5 mmHg, $p < 0.001$) but a higher central pulse pressure (37 ± 6.5 vs. 29 ± 4.7 mmHg, $p < 0.001$), maximum SBP (202 ± 20 vs. 177 ± 15 mmHg, $p < 0.001$), and ΔSBP (78 ± 19 vs. 58 ± 14 mmHg, $p < 0.001$) than females. Total vascular resistance (1293 ± 318 vs. 1218 ± 341 dyn*s/cm^5, $p = 0.369$), pulse wave velocity (6.2 ± 0.85 vs. 5.9 ± 0.58 m/s, $p = 0.079$), BP at rest (125 ± 10/76 ± 7 vs. 120 ± 11/73.5 ± 8 mmHg, $p > 0.05$), and the SBP/MET slope (5.7 ± 1.8 vs. 5.1 ± 1.6 mmHg/MET, $p = 0.158$) were not different. The SBP/W slope (0.34 ± 0.12 vs. 0.53 ± 0.19 mmHg/W) and the peak SBP/W ratio (0.61 ± 0.12 vs. 0.95 ± 0.17 mmHg/W) were markedly lower in males than in females ($p < 0.001$).

Conclusion Male athletes displayed a lower SBP/W slope and peak SBP/W ratio than females, whereas the SBP/MET slope was not different between the sexes. Vascular functional parameters were not able to predict the workload-indexed BPR in males and females.

Keywords Exercise test · Professional athletes · Sex differences · Vascular function · Workload-indexed blood pressure response

Abbreviations

ACSM	American College of Sports Medicine
Aix@75 bpm	Augmentation index at a heart rate of 75 bpm
BP	Blood pressure
BPR	Blood pressure response
CBP	Central blood pressure
DBP	Diastolic blood pressure
ECG	Electrocardiogram
MET	Metabolic equivalent of task
Peak SBP/W ratio	Ratio of systolic blood pressure and W at peak exercise
PWV	Pulse wave velocity
SBP	Systolic blood pressure
SD	Standard deviation
SBP/MET slope	Increase in systolic blood pressure per increase in metabolic equivalent of task
SBP/W slope	Increase in systolic blood pressure per increase in W
VO_{2max}	Maximum oxygen uptake

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Introduction

There is a wealth of evidence indicating a different blood pressure (BP) regulation at rest between women and men (Briant et al. 2016; Song et al. 2020). Several physiological factors have been identified that influence these differences, including sympathetic nervous activity, renin-angiotensin system, β-adrenergic vasodilatation, peripheral vascular resistance, arterial stiffening and sex hormones (Briant et al. 2016; Smith et al. 2019; Song et al. 2020; Safar et al. 2020; Ramirez and Sullivan 2018; Hermida et al. 2013; Ochoa-Jimenez et al. 2018). However, the threshold for defining hypertension was set at the same level of BP for men and women in the current guidelines (Williams et al. 2018).

The clinical impact of the blood pressure response (BPR) during exercise is another controversial issue (Sabbahi et al. 2018; Percuku et al. 2019; Hedman et al. 2019). Despite the recommendations in former guidelines (Mancia et al. 2013), which proposed different BP thresholds to define an exaggerated BPR for males and females, the European Society of Cardiology states in its latest guideline that there is currently no consensus on normal BPR during exercise (Williams et al. 2018). Thus far, the sex differences in BP regulation during exercise are not well characterized (Hedman et al. 2020; Currie et al. 2018). Though, the blood pressure response to graded clinical exercise testing offers the potential to uncover occult cardiovascular (CV) pathology and future CV risk that may go undetected by routine office measurements at rest (Caselli et al. 2019). Functional vascular impairment might lead to an exaggerated BPR to exercise even in the absence of hypertension at rest (Miyai et al. 2020; Thanassoulis et al. 2012). Novel markers of vascular function have emerged whose feasibility for acquisition at-rest via noninvasive oscillometric devices could simplify clinical assessment in uncovering this functional impairment (Miyata 2018).

Recently, a workload-indexed approach of characterizing BPR (SBP/MET slope) was introduced (Hedman et al. 2019) for the general population and for athletes (Bauer et al. 2020). Considering that a higher SBP/MET slope (> 6.2 mmHg/MET) was associated with worse survival in a normal population of male non-athletes (Hedman et al. 2019), these data suggest that a steeper increase in SBP in relation to workload is a stronger prognostic factor of mortality in males than the peak SBP. Therefore, the proposed SBP/MET slope might be a useful tool to identify individuals at risk, which would be crucial for preventive interventions.

In addition, normative age- and sex-adjusted values for new workload-indexed BPR markers such as the SBP/W slope and the peak SBP/W ratio for the general population have been published (Hedman et al. 2020). The peak SBP/W ratio represents the ratio of peak SBP to maximum achieved W in response to bicycle ergometer, whereas the SBP/W slope reflects the increase of SBP per W increment and thus the steepness of SBP in relation to workload with higher values representing a steeper increase. Of note, the presented normative values were markedly higher in females than in males, indicating a steeper BP increase during exercise (Hedman et al. 2020). These sex differences in the BP regulation are thought to be modulated by vascular function (Song et al. 2020; Haarala et al. 2020; Ayer et al. 2010; Wee et al. 2019) and thus might be revealed by measuring vascular function and central hemodynamics at rest and under exercise conditions (Hedman et al. 2020).

Given the postulated sex differences in SBP/W slope, peak SBP/W ratio and the unknown effect of sex on the SBP/MET-slope, we investigated sex differences in these markers of workload-indexed BPR in age-matched professional athletes to aid physicians in interpreting the BPR to exercise in the cardiovascular evaluation of athletes. Further, we speculated that markers of arterial stiffness, like PWV, Aix@75 and peripheral resistance, could predict the workload-indexed BPR of both sexes. In addition, we investigated the association of central hemodynamics and vascular function with the recently introduced workload-indexed markers of the BPR to exercise.

Materials and methods

Study design

The study was conducted as a cross-sectional, single-center pilot study as part of the routine pre-season medical monitoring program of the first German handball and female soccer division in July 2019. Competitive team handball and competitive soccer are both classified as high-intensity mixed sports with a high load for the cardiovascular system. They are characterized by requiring the repetition of high-intensity activities with brief recovery periods. Players need the ability to perform repeated maximal or near maximal intensities such as sprinting, jumping and changing of directions throughout the match.

All participants received a clear explanation of the study and provided their written informed consent. Further, they filled out a questionnaire regarding health status, medication, nutrition supplementation, amount of training, and history of training (pre-participation questionnaire of the European Federation of Sports medicine associations). Only healthy individuals free of underlying cardiovascular diseases, risk factors, and medication (other than oral contraceptives) were included.

The examination took place at noon between 12:00 and 14:00 o'clock and was scheduled in the first week of the new season after a 6-week competition-free interval. The last time athletes had trained was 36 h prior to the study beginning; the last allowed meal was breakfast up to 3 h before the investigation. There was no restriction of caffeine intake provided. Thus, alcohol consumption was prohibited the two days prior to the study beginning. The day before the examination was filled with commercial dates with no physical effort.

The local ethics committee approved the study protocol. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments. All subjects gave written informed consent to participate.

Study population

The participants were 72 healthy professional athletes consisting of 47 male handball and 25 female soccer players. All participants included were Caucasian, non-smokers and none took medication (except oral contraceptives) or multivitamin supplements. All female athletes were examined during the early follicular phase or in the placebo phase for those taking oral contraceptives to minimize hormonal effects. As age was found to influence the BPR to exercise in both sexes, only athletes aged 18–24 were included in the study.

All individuals were subjected to a physical examination, 12-lead electrocardiogram (ECG), and progressive maximal cycling ergometer test. Age, height, weight, and body mass index were determined. Body surface area was calculated using the formula of DuBois.

Blood pressure measurements

Resting brachial BP was measured before the exercise testing using a validated automatic device based on a standard sphygmomanometer technique (Boso clinicus, Bosch + Sohn GmbH & Co. KG, Germany). The cuff used for measurement was adjusted to the individual's arm circumference. Measurements were performed by a trained research associate on both arms in a sitting position after a resting period of 5 min and repeated after 2 min. The average BP for each arm was calculated if both measurements were within 5 mmHg. The highest value was used for statistical analyses. Athletes with a resting SBP > 140 mmHg or diastolic BP (DBP) > 90 mmHg were excluded from the study.

Exercise testing and assessment of maximum blood pressure

Athletes underwent a standardized progressive maximal cycling ergometer test with concurrent automatic brachial BP measurement and 12-lead ECG recording (Schiller AG®, Switzerland). The exercise test protocol for male athletes started with a load level of 100 W after a 2-min warm-up period that was conducted with 50 W. Female athletes started with 75 W after a warm-up period conducted with 50 W. Loads were increased by 50 W in male athletes and 25 W in females every 2 min until exhaustion, which was defined as the participant's inability to maintain the load for 2 min. Next, the load was decreased to 25 W for 3 min of active recovery that was followed by a 2-min cool-down period at rest. The test concluded with a final ECG recording and brachial BP measurement. BP was measured once a minute during test and recovery periods, including at the maximum workload, immediately after the maximum workload, immediately after the end of the test, and after 5 min of recovery. BP was measured at the right arm during the test, and the participant was instructed to let the right arm hang loosely during measurement, when possible. SBP was recorded at the appearance of the first Korotkoff sound. Each BP measurement was protocolled automatically with the corresponding time, heart rate, and workload.

Heart rate was measured during continuous ECG recording throughout the test and recovery periods. We assessed the absolute maximum workload of all athletes as well as the respective relative workload, which was adjusted to individual body weight. Other measurements included maximum heart rate, heart rate at rest, and heart rate 5 min after the exercise test. Increases in systolic and diastolic BP were calculated from peak and baseline (resting) values. Pulse pressure was calculated as SBP minus diastolic blood pressure (DBP) at rest and at maximum exercise. In addition, mean brachial BP was determined as: DBP + (SBP − DBP)/3. MET values were estimated using the standard equations of the ACSM for cycling ergometers (Thompson et al. 2013). The ΔSBP was calculated as maximum SBP-resting SBP and was indexed by the increase in MET from rest (ΔMET calculated as peak MET − 1) to obtain the SBP/MET slope (Hedman et al. 2019). The peak SBP/W ratio was determined as peak SBP/peak workload in W (Hedman et al. 2020). The SBP/W slope was calculated as the ratio of the difference in SBP from the first to the last BP measurement during exercise divided by the difference in workload in W between these two measures (last SBP − first SBP)/(last W − first W) (Hedman et al. 2020).

Non-invasive assessment of peripheral and central blood pressure and pulse pressure waveforms

We used the non-invasive vascassist2® device (isymed GmbH, Butzbach, Germany) to acquire pulse pressure waveforms by means of oscillometry. The device uses a validated model (Schumacher et al. 2018) of the arterial tree that consists of 721 electronic circuits representing all central and

peripheral arterial sections. By modulating the circuits' capacitance, resistance, inductance, and voltage, the system replicates an individual's acquired pulse pressure waves. The vascassist2® system is currently unique in the use of genetic algorithms to optimize the fidelity of the of pulse pressure wave replication (Schumacher et al. 2018). Fidelity replications of 99.6% or above were included in the analysis.

The non-invasive vascular evaluation was carried out for all participants before exercise testing. After a 15-min rest period, measurements were performed in a supine position using four conventional cuffs adapted to the upper arm and forearm circumferences of the participants. Radial and brachial pulse pressure waves were acquired on both arms with step-by-step deflation of the cuffs. The measurements took place in a room with a comfortable and stable temperature of 22 °C and a lack of external stress influences. Participants were advised not to move during the acquisition of pulse pressure waves. Two brachial and three radial measurements were performed to guarantee stable and valid results with a break of 30 s between each measurement phase. The total duration of the examination was 15 min. The acquired pulse pressure waves were then analyzed with a validated electronic model of the arterial tree to assess vascular functional parameters. Brachial and radial SBP and DBP, central systolic and diastolic blood pressure (CBP), aortic pulse wave velocity (PWV), augmentation index (Aix), augmentation index at a heart rate of 75 bpm (Aix@75), resistance index (R), total vascular resistance, and ejection duration were calculated. CBP was determined using a transfer function that was based on the peripheral arterial waveform. Calculation of Aix@75 was also based on the pulse waveform.

Statistical analysis

Descriptive analyses were carried out on all study variables for the total sample and separated by sex. All data are presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to determine normal distribution. If the data were determined to have a skewed distribution, all analyses were performed on normalized data. Between-group comparisons were made using independent sample t tests. Bivariate relations were analyzed using the Spearman correlation coefficient. Pearson's product-moment correlation coefficient was used to determine linear correlations between vascular functional parameters and exercise test results. We also performed multivariate stepwise regression analyses to explore possible linear associations across the vascular functional parameters measured at rest in both sexes, using separately the SBP/MET slope, the peak SBP/W ratio and SBP/W slope as continuous dependent variable. Statistical significance was set at $p < 0.05$ (two-tailed) for all measurements. All statistical analyses were performed using the statistical software SPSS 25.0 for Mac (Statistical Package for the Social Sciences, Chicago, IL, USA).

Results

Cohort characteristics

A total of 72 participants, consisting of 47 male and 25 female athletes, were included in the study. Male athletes were taller and heavier and displayed a greater body mass index and a higher body surface area than females. Further, the training amount per week was higher than that of females. However, age ($p = 0.365$) and history of professional training were not different between groups ($p = 0.112$). The clinical characteristics, anthropometric data, and specific training data are displayed in detail in Table 1.

Four of the examined 25 female athletes (16%) took oral contraceptives. The used hormonal contraceptives have a monophasic effect and are assigned to the fourth generation of hormonal contraceptives. They contained 3 mg drospirenone and 0.03 mg estradiol. In one case, the oral contraceptive contained 3 mg drospirenone and 0.02 mg estradiol. These combined oral contraceptive pills supply 21 days of pills with hormones followed by 7 days of hormone-free pills. This regimen is called the 21/7 regimen.

As expected, we found a significant correlation of age with history of professional training ($r = 0.959$, $p < 0.001$)

Table 1 Clinical characteristics of male ($n = 47$) and female ($n = 25$) athletes

	Male athletes $n = 47$		Female athletes $n = 25$		
	Mean	SD	Mean	SD	p value
Age (years)	21.6	1.7	21.1	2	0.365
Height (cm)	188.6	7.2	167.1	4.8	< 0.001
Weight (kg)	90.9	12.3	60.8	7.7	< 0.001
Body mass index (kg/m^2)	25.5	2.4	21.7	1.9	< 0.001
Body surface area (m^2)	2.18	0.17	1.68	0.11	< 0.001
Training history (years)	5.96	2.2	4.96	2.6	0.112
Training per week (hours)	17.85	2.9	10.8	2	< 0.001

in all athletes. Further, age was positively correlated with training per week ($r=0.226$, $p=0.013$), height ($r=0.298$, $p=0.001$), weight ($r=0.331$, $p<0.001$) and BMI ($r=0.314$ $p<0.001$). Height, weight, body surface area, and BMI all correlated positively with each other ($p<0.05$) and with the training history and the training duration per week ($p<0.05$).

Blood pressure at rest

Resting brachial BP, mean brachial BP, and brachial pulse pressure at rest were not different between male and female athletes ($p>0.05$). None of the participants displayed a BP > 140/90 mmHg. Further, heart rate at rest and central SBP were not different between the groups ($p>0.05$). Male athletes had a significantly lower central diastolic BP (< 0.001) and mean CBP ($p=0.003$) compared with female athletes. In contrast, the central pulse pressure ($p<0.001$) was higher in males than in females. Detailed data are presented in Table 2.

Resting SBP correlated positively with height, weight, BMI and sex. Resting DBP only correlated positively with age. Interestingly, central DBP was correlated with sex, but not central SBP. Further, central pulse pressure was correlated with sex.

Vascular function at rest

The aortic pulse wave velocity (PWV) was not different between male and female athletes ($p=0.079$). Further, the augmentation index at a heart rate of 75 bpm (Aix@75) ($p=0.203$), the resistance index (R) ($p=0.148$) and total vascular resistance ($p=0.369$) were not different between the groups. In addition, none of the measured parameters of vascular function at rest were correlated to sex ($p>0.05$). In contrast, PWV was correlated to age ($p<0.001$) and BMI ($p=0.044$), but not to height or weight ($p>0.05$).

In male athletes, brachial systolic blood pressure was significantly correlated to the peak SBP/W ratio. Further, in male athletes, there was significant negative correlation of brachial diastolic blood pressure with the SBP/W slope.

Table 2 Results of vascular evaluation and exercise testing in male ($n=47$) and female ($n=25$) athletes

	Male athletes $n=47$		Female athletes $n=25$		
	Mean	SD	Mean	SD	*p* value
Brachial systolic BP (mmHg)	124.8	9.9	119.6	11.1	0.057
Brachial diastolic BP (mmHg)	75.7	7.3	73.5	8.4	0.284
Mean brachial BP (mmHg)	92.1	7	88.9	7.8	0.097
Pulse pressure at rest (mmHg)	49.1	9.2	46.1	11	0.248
Heart rate at rest (bpm)	57.2	10.2	61.9	10.2	0.068
Mean aortic blood pressure (mmHg)	72.4	8.9	79.3	8.9	**0.003**
Central systolic BP (mmHg)	97.7	8.3	95.7	8.5	0.340
Central diastolic BP (mmHg)	57.2	9.5	66.6	9.5	**< 0.001**
Central pulse pressure (mmHg)	37.2	6.5	28.9	4.7	**< 0.001**
Aortic pulse wave velocity (m/s)	6.2	0.85	5.9	0.58	0.079
Augmentation index @75 bpm (%)	− 20.7	11	− 17.4	9.6	0.203
Resistance index	16.15	6.5	12.7	10.7	0.148
Total vascular resistance (dyn*s/cm^5)	1293	317.5	1218	341	0.369
Maximum heart rate (bpm)	179.3	11.8	183.5	7.8	0.079
Maximum systolic brachial BP (mmHg)	202.4	19.6	177.1	15.1	**< 0.001**
Δ systolic brachial BP (mmHg)	77.6	19.3	57.8	14	**< 0.001**
Maximum diastolic brachial BP (mmHg)	84.4	7.4	81.7	9.9	0.247
Δ diastolic brachial BP (mmHg)	8.7	9.5	8.2	8.6	0.821
Maximum pulse pressure (mmHg)	118	19.1	95.4	14.6	**< 0.001**
Absolute workload (Watt)	342	71.5	190	31.5	**< 0.001**
Relative workload (Watt/kg)	3.82	0.92	3.17	0.64	**< 0.001**
Peak energy expenditure (MET)	15.2	3.4	12.8	2.4	**0.001**
SBP/MET slope (mmHg/MET)	5.7	1.84	5.1	1.6	0.158
SBP/Watt slope (mmHg/Watt)	0.34	0.12	0.53	0.19	**< 0.001**
Peak SBP/Watt ratio (mmHg/Watt)	0.61	0.12	0.95	0.17	**< 0.001**

Bold text statistically significant differences

All other vascular functional parameters, measured at rest, were not significantly correlated to SBP/MET slope, the peak SBP/W ratio or the SBP/W slope in both male and female athletes. The results of the correlation analyses are presented in Table 3.

Heart rate and blood pressure response to exercise

Male athletes displayed a significantly higher maximum SBP, higher ΔSBP and, thus, a higher maximum pulse pressure than female athletes. In contrast, maximum heart, maximum DBP, and ΔDBP were not different between males and females (Table 2). Maximum SBP, ΔSBP, and maximum pulse pressure were correlated with sex. In contrast, maximum DBP, ΔDBP, and maximum heart rate did not vary with sex.

Performance and workload-indexed blood pressure responses

All participants completed the maximum exercise test until exhaustion, reaching a maximum heart rate above the calculated individual 85% threshold (of individually calculated maximum heart rate). Male athletes achieved a significantly higher absolute workload than female athletes with a correspondingly higher relative workload and MET.

The SBP/W slope (0.34 ± 0.12 vs. 0.53 ± 0.19 mmHg/W, $p < 0.001$) and the peak SBP/W ratio (0.61 ± 0.12 vs. 0.95 ± 0.17 mmHg/W, $p < 0.001$) were significantly lower in male athletes than in female athletes. However, the SBP/MET slope was not different between males and females (5.7 ± 1.84 vs. 5.1 ± 1.6 mmHg/MET, $p = 0.158$) (Table 2).

The SBP/W slope ($r = 0.633$, $p < 0.001$) and the peak SBP/W ratio ($r = 0.761$, $p < 0.001$) were correlated with sex, but the SBP/MET slope ($r = -0.162$, $p = 0.178$) was not.

The SBP/MET slope was positively correlated with height ($r = 0.257$, $p = 0.030$), weight ($r = 0.326$, $p = 0.006$), and BMI (0.322, $p = 0.006$) but not with age ($r = 0.077$, $p = 0.407$).

In contrast, the SBP/W slope was negatively correlated with age ($r = -0.233$, $p = 0.010$), height ($r = -0.573$, $p < 0.001$), weight ($r = -0.571$, $p < 0.001$), and BMI ($r = -0.459$, $p < 0.001$).

Further, negative correlations of the peak SBP/W ratio with height ($r = -0.691$, $p < 0.001$), weight ($r = 0.691$, $p < 0.001$), and BMI (-0.483, $p < 0.001$) were found.

Table 3 Pearson's correlations of the results of the vascular evaluation with the SBP/MET slope, the SBP/W slope and the peak SBP/W ratio for male and female athletes

	SBP/MET	SBP/W slope	peak SBP/W ratio
Male athletes			
Brachial systolic BP (mmHg)	0.073 (0.627)	0.025 (0.868)	**0.329 (0.024)**
Brachial diastolic BP (mmHg)	− 0.270 (0.067)	**− 0.342 (0.019)**	− 0.139 (0.350)
Mean aortic blood pressure (mmHg)	0.081 (0.589)	0.007 (0.964)	0.041 (0.787)
Central systolic BP (mmHg)	0.185 (0.214)	− 0.041 (0.783)	− 0.021 (0.888)
Central diastolic BP (mmHg)	− 0.055 (0.711)	− 0.128 (0.390)	− 0.076 (0.611)
Central pulse pressure (mmHg)	0.060 (0.669)	0.108 (0.469)	0.117 (0.432)
Aortic pulse wave velocity (m/s)	− 0.123 (0.412)	− 0.240 (0.104)	− 0.307 (0.063)
Augmentation index @75 bpm (%)	0.001 (0.996)	0.053 (0.725)	− 0.012 (0.934)
Total vascular resistance (dyn*s/cm^5)	− 0.084 (0.575)	− 0.167 (0.262)	− 0.172 (0.248)
Resistance index	− 0.079 (0.596)	− 0.177 (0.233)	− 0.288 (0.058)
Female athletes			
Brachial systolic BP (mmHg)	− 0.239 (0.261)	− 0.125 (0.550)	− 0.162 (0.439)
Brachial diastolic BP (mmHg)	0.238 (0.262)	0.247 (0.234)	0.242 (0.244)
Mean aortic blood pressure (mmHg)	0.082 (0.703)	− 0.161 (0.443)	− 0.160 (0.445)
Central systolic BP (mmHg)	0.056 (0.794)	− 0.206 (0.322)	− 0.199 (0.340)
Central diastolic BP (mmHg)	0.109 (0.611)	− 0.143 (0.494)	− 0.143 (0.494)
Central pulse pressure (mmHg)	0.009 (0.966)	− 0.037 (0.861)	− 0.019 (0.928)
Aortic pulse wave velocity (m/s)	− 0.263 (0.204)	0.071 (0.735)	0.128 (0.543)
Augmentation index @75 bpm (%)	− 0.190 (0.374)	− 0.155 (0.458)	− 0.169 (0.420)
Total vascular resistance (dyn*s/cm^5)	− 0.060 (0.782)	− 0.327 (0.111)	− 0.327 (0.111)
Resistance index	− 0.305 (0.147)	− 0.290 (0159)	− 0.308 (0.134)

Bold text signifies significant correlations

The SBP/MET slope was the only workload-indexed marker of BPR that was not correlated with both age and sex.

Regression analyses of the influence of the hemodynamic data of athletes on different markers of workload-indexed blood pressure response

We performed multivariate regression analyses to explore possible linear associations across the vascular functional parameters measured at rest in both sexes with the workload-indexed markers of BPR. We used brachial systolic BP, brachial diastolic BP, central systolic and diastolic BP, mean central BP, central pulse pressure, PWV, Aix@75 bpm, R and total vascular resistance as predictors of the regression model and, separately, the SBP/MET slope, the peak SBP/W ratio and SBP/W slope as continuous dependent variable in both sexes. All evaluated regression models were not able to predict the markers of workload-indexed BPR in both sexes and neither of the evaluated vascular functional parameters at rest were found to be independent determinants of the workload-indexed BPR. Details of the respective regression analyses are presented in Table 4.

Discussion

The present study is, to our knowledge, the first to investigate sex differences in markers of workload-indexed BPR and their correlations with parameters of vascular function in age-matched professional athletes.

Our most important findings are that,

(1) The SBP/W slope and the peak SBP/W ratio were significantly different between female and male athletes whereas the SBP/MET-slope was not different.
(2) The SBP/W slope and peak SBP/W ratio was significantly higher in females despite males displaying a significantly higher maximum SBP.
(3) None of the parameters of vascular function at rest predicted these gender-based differences.

These findings imply different physiological adaptations of BPR to exercise between females and males that are not revealed with the measurement of central hemodynamics and vascular function at rest.

In general, given different exercise testing methods (Weiss et al. 2010; Jae et al. 2015), BP measurement methods (Weiss et al. 2010; Hedman et al. 2019) and determinations of SBP at maximum (Hedman et al. 2019; Bauer et al. 2020; Pressler et al. 2018; Caselli et al. 2016) or submaximal (Weiss et al. 2010) workload, a comparison across studies is challenging. Further, studies investigating the BPR to exercise in athletes are sparse (Pressler et al. 2018; Caselli et al. 2016) and workload-indexed data for female athletes are not available, so far.

Our study provides the first comparison of the newly introduced markers of workload-indexed BPR to exercise in male and female professional athletes.

Recently, Hedman et al. (2020) reported age- and sex-specific reference equations for workload-indexed systolic BPR during bicycle ergometry for the general population.

The SBP/W slope, reflecting the increase of SBP per W increment and thus the steepness of SBP in relation to workload, was reported to be markedly higher in females than in males (Hedman et al. 2020), indicating a different physiological adaptation of SBP to exercise (Smith et al. 2019; Wheatley et al. 2014; Hedman et al. 2020). In line with this, female athletes of our study displayed a significant higher SBP/W slope compared to male athletes.

These sex differences in the SBP/W slope indicates women's need for a larger relative increase in cardiac output to generate the same power output (Joyner et al. 2016; Wheatley et al. 2014). In consequence, lower achieved absolute and relative workloads in women were partly explained with different body composition, especially lower lean muscle mass compared to men (Wheatley et al. 2014; Joyner et al. 2016; Song et al. 2020; Samora et al. 2019).

Another interesting influencing factor that attributes to the different BPR in women compared to men was identified

Table 4 Stepwise multivariate regression analyses of the results of the vascular evaluation with the SBP/MET slope, the SBP/W slope and the peak SBP/W ratio as continuous dependent variable for male and female athletes

	Male athletes			Female athletes		
	R^2	F	p value	R^2	F	p value
SBP/MET slope	0.161	$F(8, 38) = 2.101$	0.060	− 0.214	F(8, 15) = 0.493	0.843
SBP/W slope	0.139	$F(8, 38) = 1.928$	0.084	0.130	$F(8, 16) = 0.656$	0.722
Peak SBP/W ratio	0.170	$F(10, 36) = 1.942$	0.071	− 0.114	$F(10, 14) = 0.754$	0.668

Predictors of the model were brachial systolic BP, brachial diastolic BP, central systolic and diastolic BP, mean central BP, central pulse pressure, PWV, Aix@75 bpm, R and total vascular resistance

with different metaboreceptor stimulation in women (Samora et al. 2019). Notably, in pre-menopausal women, beta-adrenergic sensitivity is enhanced compared to men which blunts vasoconstrictor response due to concurrent beta-adrenergic mediated vasodilation (Song et al. 2020) during constant-load submaximal exercise and consequently leads to a limitation in stroke volume (Wheatley et al. 2014).

Though, at the highest exercise intensities, a metaboreflex-driven increase in peripheral resistance is observed (Augustyniak et al. 2001; Smith et al. 2019), which may be altered in trained women compared to untrained women. These deliberations might partly explain the differences in the SBP/W slope of our female athletes (0.53 ± 0.19 mmHg/W) compared to the proposed normative 50th percentile of 0.38 ± 0.14 mmHg/W of the Hedman cohort (Hedman et al. 2020). Hence, it can be speculated that higher fitness levels, and thus enhanced abilities to maintain physical performance, contribute to a higher SBP/W slope in athletic women.

In contrast and in line with the aforementioned, the BPR to exercise in men is characterized by an increase in cardiac output and by an increase in total peripheral resistance (Samora et al. 2019) and therefore less influenced by fitness levels. Hence, the values of our male athletes were comparable (0.34 ± 0.12 vs. 0.33 ± 0.11 mmHg/W) to the proposed reference values of the general population.

These findings of sex differences in BPR to exercise in both trained and untrained individuals indicate a different BP regulation during exercise between men and women that is irrespective of fitness levels, complex and not yet fully understood (Samora et al. 2019; Joyner et al. 2016).

Further, these considerations might also explain the sex differences in the peak SBP/W ratio, which were described by Hedman et al. (2020) and even were apparent in our study cohort of professional athletes. The peak SBP/W ratio showed markedly higher values in women of both studies. The larger peak SBP/W ratio at a lower absolute peak SBP in women compared to men hints at men's capacity to extract a relatively large increase in power output (once cardiac reserve for cardiac output has been reached) from the exercise pressor reflex-generated increase in the sympathetic outflow that increases perfusion pressure by increasing total vascular resistance.

In line with the aforementioned, the absolute values of the peak SBP/W ratio in our cohort of professional athletes were lower compared to the published reference values (Hedman et al. 2020). Given that our athletes had significantly greater cardiorespiratory fitness (CRF) than the participants of the Hedman study (3.82 W/kg vs. 2.8 W/kg and 3.17 W/kg vs. 2.08 W/kg for males and females, respectively) it is tempting to speculate that CRF affects the SBP/W slope differently in men and women. Hence, the peak SBP/W ratio of athletes might be lower compared to that of controls, as athletes usually achieve higher workloads. In consequence, these results raise the question whether athletes might need different thresholds for the peak SBP/Watt ratio. Thus far, the presented reference values of the peak SBP/W ratio for the general population should not be used as the only workload-indexed marker of BPR in the interpretation of exercise testing of professional athletes of both sexes.

In contrast to the SBP/W slope and the peak SBP/W ratio, we could not detect significant sex differences in the SBP/MET slope.

Unlike the SBP/W slope and the peak SBP/W ratio, the SBP/MET slope is unaffected by bodyweight as METs are corrected for body weight. Hence, division of the change of SBP by this ratio informs about the rate of blood pressure change relative to an increase of exercise intensity above the resting baseline. This explains why there was no significant difference in SBP/MET slope between our female and male athletes (5.1 mmHg vs. 5.7 mmHg in females and males, respectively). In another study a median of 6.4 mmHg/MET in a male cohort of a general population (Hedman et al. 2019) was reported, indicating that the proposed threshold of 10 mmHg/MET (Thompson et al. 2013) represents an upper limit rather than an average normal increase. Considering that a higher SBP/MET slope (> 6.2 mmHg/MET) was associated with worse survival in a normal population of male non-athletes (Hedman et al. 2019), the proposed SBP/MET slope might help to identify individuals at risk, which would be crucial for preventive interventions.

Given its apparent independence of gender the SBP/MET slope may be already used for the interpretation of the BPR to exercise in athletes of both sexes during the pre-participation screening. Notably, the SBP/MET slope was the only evaluated workload-indexed parameter of our study that was not different between male and female athletes.

Thus, the proposed normative values were derived from 285 males and 97 females in the Hedman cohort (Hedman et al. 2020), and the prognostic value of the SBP/W slope, the peak SBP/W ratio and the SBP/MET slope needs to be confirmed in the future.

As described above, the complex and ambiguous association between the BPR to exercise and cardiovascular risk might be explained with vascular function and vascular adaptation to exercise (Green et al. 2012). Further, increased arterial stiffness was related to an exaggerated BPR in a general population (Thanassoulis et al. 2012), and PWV was able to predict the BPR to exercise in healthy young adults (Haarala et al. 2020). Thus, in our cohort of highly trained male and female athletes, we did not detect differences, despite our attempt to minimize potentially confounding influences of the menstrual cycle.

Hence, the influence of oral contraceptives (OCP) of the fourth generation that were taken by four athletes seems unlikely, as these OCP are currently seen not to affect

peripheral vasculature (Williams and MacDonald 2020) or BP negatively (Ribeiro et al. 2018).

Another confounding factor that may have influenced the measurements of PWV and BP are postprandial effects, especially raised serum triglycerides and lipemia. Thus far, previous studies concerning this topic have yielded inconsistent results (Taylor et al. 2014; Lithander et al. 2013) and data for professional athletes are sparse. In healthy young individuals (mean age 25.6 years) no measureable increase in PWV after a mixed meal high in saturated fat were found (Taylor et al. 2014), indicating that postprandial effects are unlikely to influence our findings.

The PWV we determined in our athletes is in line with other studies that investigated athletes (Vlachopoulos et al. 2010; Bauer et al. 2019) and with recent meta-analyses (Ashor et al. 2014). Global vascular resistance at rest, R, and PWV at rest were not different between male and female professional athletes in our current study, and, consequently, they were not able to predict the workload-indexed markers of BPR. In addition, all central hemodynamic parameters, determined at rest, did not correlate with the workload-indexed markers of BPR and were not able to predict them.

In conclusion, it may be speculated that resistance index and global vascular resistance differ during exercise conditions and lead to the detected difference in the workload-indexed BPR with male athletes displaying a higher arterial vasodilator reserve compared to women. Unfortunately, vascular resistance could not be measured during exercise to substantiate this hypothesis. Taken together, these results highlight the problems inherent to the use of non-invasive devices that evaluate vascular function via oscillometry (Miyata 2018). These validated methods deliver reliable results at rest, but not during an exhaustive exercise test (Miyata 2018).

Our study has attempted to identify reliable sex differences in vascular functional parameters at rest to predict the workload-indexed BPR to a maximum exercise test. However, this was not the case, and even PWV was not different. As total vascular resistance at rest and SBP were not different between male and female athletes, our data indicate the importance of the different vascular functional regulation during exercise for the BPR to exercise in both sexes.

Limitations and strengths

Our study has a few limitations. The number of participants limited its power to uncover potential correlations between the workload-indexed BPR parameters measured and markers of cardiac and vascular function other than CBP, PWV, total vascular resistance, brachial BP, and the BPR to a maximum exercise test. The focus on professional soccer and handball athletes may limit extrapolation of the results to other sport disciplines; however, as these team sports expose athletes to the hemodynamic stress of frequent interval sprints, it is representative of other sports with a high dynamic component (> 75% VO_{2max}) and a moderate static component (10–20%) (Levine et al. 2015). Another limitation is the difference in training hours per week between males and females that may have influenced the results. Thus, female athletes in team sports usually display lower training volumes per week than their male peers. Further, we did not control for diet and potential postprandial effects, body composition, and ventricular function. Our exclusive focus on young male and female athletes precludes the extrapolation of our results to athletes of other age groups. However, we included professional male and female athletes of the same age without cardiovascular disease and free of medication, and we controlled for the menstrual cycle to minimize confounders. Thus, four female athletes were taking oral contraceptives of the fourth generation, which might have influenced the BP. Further, the rigid design of measuring vascular function and accomplishing an exhaustive and standardized exercise test in both sexes must be mentioned. Therefore, our cohort of professional handball and soccer athletes, although small, was homogeneous, which strengthens our analysis.

Conclusion

In our cohort of professional athletes, we detected sex differences in the SBP/W slope and the peak SBP/W ratio, with a steeper BP increase in females. In contrast, we identified the SBP/MET slope as a sex-independent marker of workload-indexed BPR. Despite sex differences in central hemodynamics and vascular function measured at rest, these parameters were not able to predict any of the workload-indexed markers of BPR in males and females. These findings emphasize the link between vascular function, total vascular resistance, BPR, and physical performance during exercise in athletes. Further, a sex-specific consideration of BPR to exercise testing, which is frequently performed in the cardiovascular evaluation of competitive athletes, is encouraged to identify athletes at risk.

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