Relationship between Hypercoagulability and Mesenteric Ischemia early after Cardiac Surgery

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1. Preface

Meeting presentation

The results of this investigation were presented at the 54th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery (17. February 2025 in Hamburg, Germany).

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2. Introduction

2.1 Epidemiology of Mesenteric Ischemia

Demographic correlates

Mesenteric ischemia is a serious clinical scenario characterized by reduced perfusion of the intestine. As a result of this reduced perfusion, tissue ischemia occurs, which can lead to potentially life-threatening complications if left untreated. The development of this disease is influenced by a variety of demographic and clinical factors, the early identification of which is crucial for timely diagnosis and effective initiation of therapy. In the following, a detailed analysis of these influencing factors is presented using current scientific evidence.

Advanced age is considered a significant demographic risk factor for the development of mesenteric ischemia. Numerous studies consistently show that older patients are at increased risk of both the onset and progression of this disease. For example, in the study by Fatma et al. (2024), significantly increased mortality was observed in patients over 60 years of age; in this age group, the mortality rate was 88%. A systematic review by Wu et al. (2022) also confirms that mesenteric ischemia occurs predominantly in older patients, who often suffer from multiple comorbidities. The increased vulnerability of this patient group can be attributed to age-related vascular remodeling processes such as atherosclerosis, which increase the likelihood of arterial occlusion.

The available data do not show any clear trends with regard to sex-specific differences in the risk for mesenteric ischemia. While some studies describe a slightly higher incidence in women, these differences usually prove to be insignificant. For example, Fatma et al. (2024) reported that there is no statistically significant difference in mortality rates between men and women. Li et al. (2022) observed a higher number of female patients in their modeling group, but did not find any significant outcome differences. These results suggest that sex does not have an independent predictive value for the development or prognosis of mesenteric ischemia.

To date, there is limited knowledge of ethnic and geographical differences. Echeverría et al. (2023) pointed out in their paper that individuals of Caucasian descent may be at increased risk of developing mesenteric ischemia. However, this hypothesis requires further validation by more comprehensive population-based studies.

Clinical determinants

Cardiovascular disease is one of the most important clinical risk factors for mesenteric ischemia. Pathologies such as atrial fibrillation, arterial hypertension, and peripheral arterial occlusive disease are associated with a significantly increased incidence. Echeverría et al. (2023) highlighted in particular the importance of atrial fibrillation, which often leads to mesenteric artery occlusion due to the formation of emboli. Similarly, the meta-analysis by Wu et al. (2020) identified peripheral arterial occlusive disease as an independent risk factor for short-term postoperative mortality in patients with mesenteric ischemia.

Hypercoagulable states also play a crucial role in the pathogenesis of the disease. Conditions such as thrombophilia, deep vein thrombosis, or malignant diseases can promote the development of venous thrombosis in the mesenteric region. Fatma et al. (2024) described in their study that patients with a history of thromboembolic events in particular had an increased probability of developing mesenteric ischemia.

Another critical clinical feature is the presence of shock or hemodynamic instability. These conditions are strongly associated with a poor prognosis. Fatma et al. (2024) reported a mortality rate of 94.4% in patients who presented in a state of shock. Li et al. (2022) also demonstrated that shock is an independent risk factor for the onset of intestinal infarction in acute mesenteric ischemia. The presence of shock is usually an expression of an advanced stage of the disease with a high probability of irreversible intestinal necrosis.

Chronic comorbidities such as diabetes mellitus, chronic kidney disease, or heart failure are common comorbidities in patients with mesenteric ischemia and are associated with an unfavorable prognosis. Kumar et al. (2023) were able to show that patients with end-stage renal disease have a significantly increased mortality. These findings are consistent with the findings of Wu et al. (2020), who identified kidney disease as an independent risk factor for short-term postoperative mortality.

2.2 Mesenteric ischemia after cardiac surgery

Mesenteric ischemia is a rare but highly threatening complication following cardiac surgery. Due to its prognostic relevance for the survival and long-term quality of life of patients, it

requires special attention. The following is a comprehensive analysis of the frequency, clinical course, and predictive factors of this complication, supported by the currently available evidence.

Epidemiological characteristics

The incidence of mesenteric ischemia after cardiac surgery varies in the literature, but remains low overall. Reported frequencies range from 0.09% to 0.86% in patients undergoing cardiac surgery (Edwards et al., 2005; Eris et al., 2013; Nilsson et al., 2013). In patients who undergo heart surgery using the cardiopulmonary bypass (CPB), the incidence is about 0.49% (Venkateswaran et al., 2002). Non-occlusive mesenteric ischemia (NOMI) is the most common form, accounting for 45% to 79.2% (Petrov et al., 2024; Sakamoto et al., 2020).

Although the incidence appears low, the severity of the disease should not be underestimated. Affected patients usually belong to high-risk groups with multiple comorbidities, which significantly worsens the prognosis.

Prognostic parameters and risk stratification

The prognosis after mesenteric ischemia following cardiac surgery is generally unfavorable, with mortality rates varying considerably: reported mortality ranges from 44% to 91%, with an average of about 60 to 70% (Edwards et al., 2005; Petrov et al., 2024; Yuan, 2022; Klempnauer et al., 1997). The chances of survival are significantly better if the ischemic damage is limited to a single intestinal segment; extensive ischemia, on the other hand, is often lethal (Edwards et al., 2005; Hasan et al., 2004). The timing of the therapeutic intervention has a decisive influence on the prognosis. Early interventions, especially in the form of laparotomy, improve survival rates. Nevertheless, mortality remains high even with rapid initiation of therapy (Abboud et al., 2008; Hasan et al., 2004).

Numerous preoperative, intraoperative, and postoperative risk factors have been identified as prognostically unfavorable. Preoperative factors include advanced age (Eris et al., 2013; Nilsson et al., 2013), the presence of peripheral arterial occlusive disease (Venkateswaran et al., 2002; Byhahn et al., 2001), and a reduced left ventricular ejection fraction (LVEF)

(Ponomareva et al., 2024; Eris et al., 2013) as well as pre-existing renal insufficiency or dialysis (Miyagawa et al., 2022; Takeyoshi et al., 2022). Intraoperative factors with a negative influence on the prognosis include a prolonged duration of cardiopulmonary bypass (Venkateswaran et al., 2002; M et al., 2002) and the use of an intra-aortic balloon pump (IABP) (Venkateswaran et al., 2002; M et al., 2002). Postoperatively, elevated serum lactate in particular constitutes a critical marker (Krasivskyi et al., 2023; Byhahn et al., 2001). The need for high doses of vasopressors or inotropes (Ponomareva et al., 2024; Wiesmueller et al., 2022) and the occurrence of acute kidney failure or multi-organ failure also significantly worsen the prognosis (Edwards et al., 2005; Miyagawa et al., 2022).

Pathophysiological cascades and clinical implications

Mesenteric ischemia after cardiac surgery is caused by multifactorial mechanisms. Non-occlusive mesenteric ischemia (NOMI) is the most common pathomechanism and usually results from reduced splanchnic perfusion due to low cardiac output or drug-induced vasospasms (Petrov et al., 2024; Idhrees et al., 2022). Less commonly, mesenteric ischemia is due to embolic events, which can occur especially in atrial fibrillation or the presence of intracardiac thrombi (Klempnauer et al., 1997). Even rarer is mesenteric venous thrombosis, which is observed in patients with hypercoagulable conditions (Idhrees et al., 2022).

The implications of mesenteric ischemia extend beyond the immediate clinical course. Patients who survive this complication often require lengthy follow-up, sometimes with renewed surgical interventions and intensive rehabilitative therapy. The gastrointestinal sequelae are often severe and significantly impair the quality of life (Petrov et al., 2024).

In addition, there is an urgent need for optimized diagnostic strategies. The previously dominant dependence on invasive procedures such as mesenteric angiography often leads to a delay in the initiation of therapy, which is particularly critical in view of the high mortality rate in cases of delayed intervention (Schütz et al., 1998; Wiesmüller et al., 2022). A deeper understanding of the complex risk constellations – especially with regard to advanced age and underlying vascular diseases – could help to clarify preoperative risk assessments and develop individualized prevention strategies for particularly vulnerable patient groups (Wiesmüller et al., 2022).

2.3 Diagnosis of Mesenteric Ischemia

Early and accurate diagnosis is key to improving clinical outcomes for affected patients. Delays in diagnostics are associated with a significantly increased mortality rate. The following is an overview of current diagnostic methods for the detection of mesenteric ischemia, taking into account both their areas of application and limitations.

2.3.1 Clinical presentation

Delayed clinical presentation is a highly relevant prognostic factor in mesenteric ischemia, which is associated with significantly increased mortality. In their paper, Fatma et al. (2024) emphasize the essential importance of early diagnosis and therapeutic intervention, as a delayed presentation to the hospital has a direct negative impact on survival. Similarly, Dhamnaskar et al. (2016) found that a presentation delay of more than 24 hours is an independent negative predictor of mortality in patients with acute mesenteric ischemia.

Diagnosing mesenteric ischemia following cardiovascular surgery is a significant clinical challenge. This is primarily due to the non-specific symptoms and the critically unstable condition of the affected patients. Patients often present with abdominal pain, distended abdomen, and paralytic ileus. However, these findings are not diagnostically significant, as they occur in a variety of other abdominal diseases (Idhrees et al., 2022; Garofalo M et al., 2002). Gastrointestinal bleeding or diarrhea are less common, but they may nevertheless accompany reduced mesenteric perfusion (Byhahn et al., 2001).

Contrast-enhanced computed tomography (CT) is the most widely used imaging method. Nevertheless, there is a limitation that in particular non-occlusive forms of ischemia can be overlooked (Idhrees et al., 2022; Yuan, 2022). In many cases, therefore, a diagnostic laparoscopy or laparotomy is required to verify the suspected diagnosis (Abboud et al., 2008; Hasan et al., 2004).

The determination of serum lactate levels serves as a non-specific marker for reduced intestinal perfusion. An elevated lactate level may correlate with the extent of ischemia, but does not have sufficient specificity alone to enable a diagnosis (Krasivskyi et al., 2023; Byhahn et al., 2001). Likewise, elevated serum creatinine levels are considered a negative prognostic marker and reflect the presence of acute or chronic renal insufficiency, which is often associated with multi-organ failure (Miyagawa et al., 2022).

In summary, it can be stated that the early identification and diagnosis of mesenteric ischemia after cardiac surgery is considerably complicated by the complex clinical presentation and the limited diagnostic specificity of the available parameters. Interdisciplinary cooperation and a high level of clinical awareness of this rare but serious complication are therefore indispensable.

2.3.2 Laboratory diagnosis

A large number of laboratory analytical parameters correlate with the occurrence and progression of mesenteric ischemia. The most common findings in these patients include pronounced leukocytosis, metabolic acidosis, and elevated lactate levels. In their study, Li et al. (2022) identified a leukocyte count of $\geq 18 \times 10^9$/L as a significant risk factor for the occurrence of an intestinal infarction. Similarly, the analysis by Calame et al. (2022) showed that lactate levels above 7 mmol/L are predictive of 28-day mortality in non-occlusive mesenteric ischemia.

In addition to the classic laboratory parameters, biomarkers are increasingly becoming the focus of research, especially for the differentiation of ischemic processes with and without transmural necrosis. The human intestine is not only a central organ for nutrient absorption, but also acts as an indicator of systemic homeostasis. Intestinal fatty acid-binding protein (I-FABP) plays a key role in this function. This cytosolic protein, localized in the enterocytes of the intestinal epithelium, is primarily responsible for the intracellular transport of long-chain fatty acids (**Figure 1**). In addition, it has established itself as a valid clinical marker for ischemia-related epithelial damage. The biological versatility of this molecule extends across physiological, pathophysiological, and pharmacological domains. Recent studies have investigated the role of biomarkers such as plasma citrulline and I-FABP in the diagnosis of mesenteric ischemia. In particular, increased concentrations of I-FABP were associated with the detection of intestinal necrosis. In addition, this biomarker allows differentiation between ischemic processes with and without tissue necrosis (Bourcier et al., 2022).

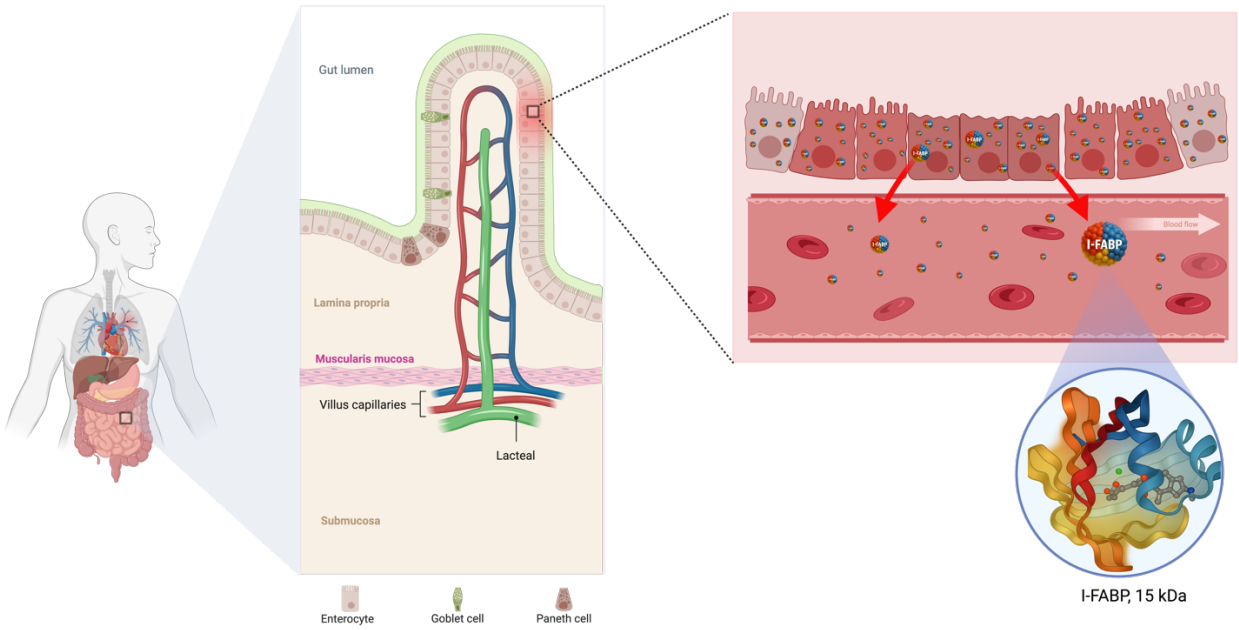

Figure 1. Release of I-FABP in intestinal ischemia and epithelial damage.

Legend: The scheme shows the localization and release of the *intestinal fatty acid-binding protein* (I-FABP) from enterocytes of the small intestinal mucosa. In the healthy state, I-FABP is localized intracellularly in enterocytes. In cases of epithelial damage, such as that which occurs due to ischemic processes, the cell membranes are destroyed. I-FABP is thus released into the extracellular space and subsequently enters the bloodstream. This makes I-FABP a sensitive and early biomarker for the detection of intestinal ischemia. The blue-red-yellow (tricolor) dots represent I-FABP molecules. (Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/qzo7eqa)

Despite the diagnostic potential of I-FABP, its use still has limitations in terms of sensitivity and specificity, especially with regard to different forms of ischemia (Bourcier et al., 2022). Additional studies are needed to substantiate the clinical validity and significance of these biomarkers in diverse patient populations and different care settings (Bourcier et al., 2022).

Overall, laboratory chemical parameters and innovative biomarkers can provide valuable diagnostic and prognostic information in patients with suspected mesenteric ischemia. Their importance lies not only in risk assessment, but also in dynamic assessment of the course of the condition and treatment decisions.

2.3.3 Functional diagnostics methods

Imaging techniques, especially CT, play a central role in the diagnosis of mesenteric ischemia. In a study by Li et al. (2022), characteristic intestinal changes such as thickening of the intestinal wall and intestinal pneumatosis were described as significant predictors of an intestinal

infarction. Emile (2018) was also able to demonstrate on CT scans that combined thrombosis of the portal vein and the superior mesenteric vein is an independent predictor of transmural intestinal necrosis.

Ultrasound

Sonography, especially Doppler sonography, is a non-invasive and cost-effective method for assessing mesenteric perfusion. It allows a real-time representation of vascular patency and intestinal wall perfusion without radiation exposure (Orihashi, 2023).

The informative value of sonography depends to a large extent on the level of experience of the examiner; insufficient expertise can lead to misinterpretation (Orihashi, 2023). In addition, the penetration depth of the ultrasound waves is limited, which significantly limits image quality, especially in obese patients or in those with meteorism (Orihashi, 2023).

Gold standard – Computed Tomography Angiography (CTA)

CTA is considered the imaging gold standard in the diagnosis of mesenteric ischemia. It enables a high-resolution visualization of the arterial and venous supply of the gastrointestinal tract. This allows occlusions, thromboses, and stenoses to be identified and the extent of ischemic intestinal involvement to be assessed, which in turn makes it possible to differentiate between forms of ischemia that can be treated surgically and those that are managed conservatively (Ronza et al., 2024; Kuznetsov et al., 2024).
Early radiological findings are crucial for timely diagnosis. The most important predictors include:

- *Intestinal changes on CT*: Thickening of the intestinal wall, the presence of intestinal pneumatosis, and intramural bleeding suggest ischemia (Li et al., 2022; Emile, 2018).
- *Combined thrombosis of the portal vein and the superior mesenteric vein*: This constellation is considered a strong indicator of transmural necrosis (Emile, 2018).
- *Free intraperitoneal fluid*: Its detection in imaging correlates with an advanced stage of the disease and an unfavorable prognosis (Emile, 2018).

Repeated use of CTA leads to significant radiation exposure and can lead to contrast-media-induced nephropathy if there is pre-existing renal insufficiency (Orihashi, 2023). In individual cases, ischemic necrosis may be present despite well-contrasted mesenteric vessels, leading to a false sense of security (Orihashi, 2023). In emergency situations or in structurally less well-

equiped regions, the availability of CTA is often limited, making timely diagnostics difficult (Orihashi, 2023).

2.3.4 Invasive diagnosis

Gastro-colonoscopy

Endoscopy plays an important role in the diagnosis and follow-up of mesenteric ischemia. Endoscopy, ideally combined with other imaging techniques, allows the visualization of mucosal changes, although its access to distal intestinal sections is limited. This highlights the need for an integrative diagnostic strategy.

Typical endoscopic findings include edema, erythema, and mucosal atrophy. In individual cases, superficial ulcerations can also be detected. In a patient with postprandial pain and melena, a pale-appearing mucosa with ulcers, suggestive of ischemia, was identified endoscopically (Segura et al., 2022).

Endoscopic diagnostics are limited, especially for distal sections of the intestine. An inconspicuous endoscopic finding therefore by no means excludes mesenteric ischemia (Segura et al., 2022). Specialized endoscopic methods such as laser Doppler flowmetry or visible light spectroscopy have the potential to increase diagnostic accuracy and provide valuable additional information, especially in chronic cases (Berge et al., 2019).

Surgical diagnostics – laparotomy

Intraoperative diagnostic procedures, especially second-look surgeries, are essential for the precise assessment of the extent of ischemic damage and for the monitoring of revascularization. Techniques such as optical coherence tomography (OCT) are currently being investigated for their potential to provide high-resolution intraoperative images of intestinal microvasculature (Baleev et al., 2020). The invasiveness of repeated surgical procedures, however, increases the risk of complications and is associated with longer convalescence (Baleev et al., 2020). Furthermore, the use of highly specialized techniques such as OCT is resource-intensive and requires both special technical equipment and experienced personnel, which limits their application in many centers (Baleev et al., 2020).

2.3.5 Dependent histopathological alterations in intestinal tissue

The subsequent deprivation of oxygen and metabolic substrates leads to a rapid and temporally structured progression of cellular and tissue injury during complete cessation of arterial flow to the intestinal tract. Histopathological changes occur in distinct stages, tightly correlated with the duration of ischemia, as illustrated in **Figure 2**.

As early as 15 minutes following the onset of ischemia, initial structural alterations in the intestinal mucosa can be observed. Histologically, these manifest as apical enterocyte disintegration, epithelial cell swelling, and early crypt epithelial detachment. Although clinical symptoms may still be absent during this phase, the disruption of epithelial integrity signals the beginning of a critical cellular imbalance and impending mucosal injury (Udassin et al., 1994).

At approximately 3 hours of continuous ischemia, mucosal exfoliation becomes evident. This phase is defined by the extensive detachment of the epithelial lining from the basal lamina. Despite the severity of mucosal disruption, this stage may still be reversible with prompt reperfusion and appropriate medical intervention. However, intestinal barrier function is severely compromised, facilitating bacterial translocation and endotoxemia, which contribute to systemic inflammation and sepsis (Udassin et al., 1994).

Beyond 6 hours of persistent ischemia, the damage progresses to transmural necrosis, an unequivocal indicator of irreversible tissue injury. Histopathologically, this stage is characterized by coagulative necrosis of all layers of the intestinal wall, including the muscularis propria and serosa. Clinically, this is accompanied by sudden deterioration, with the development of intestinal gangrene, perforation, and peritonitis. At this point, urgent surgical intervention becomes imperative, as mortality rates escalate dramatically (Udassin et al., 1994).

This time-dependent model underscores the crucial role of early recognition and therapeutic intervention in the management of acute mesenteric ischemia. The therapeutic window narrows significantly within the first hours of ischemia, reinforcing the need for rapid diagnostic and treatment strategies. These findings are consistent with the experimental data reported by Udassin et al. (1994), who demonstrated that irreversible ischemic injury typically ensues between 3 and 6 hours.

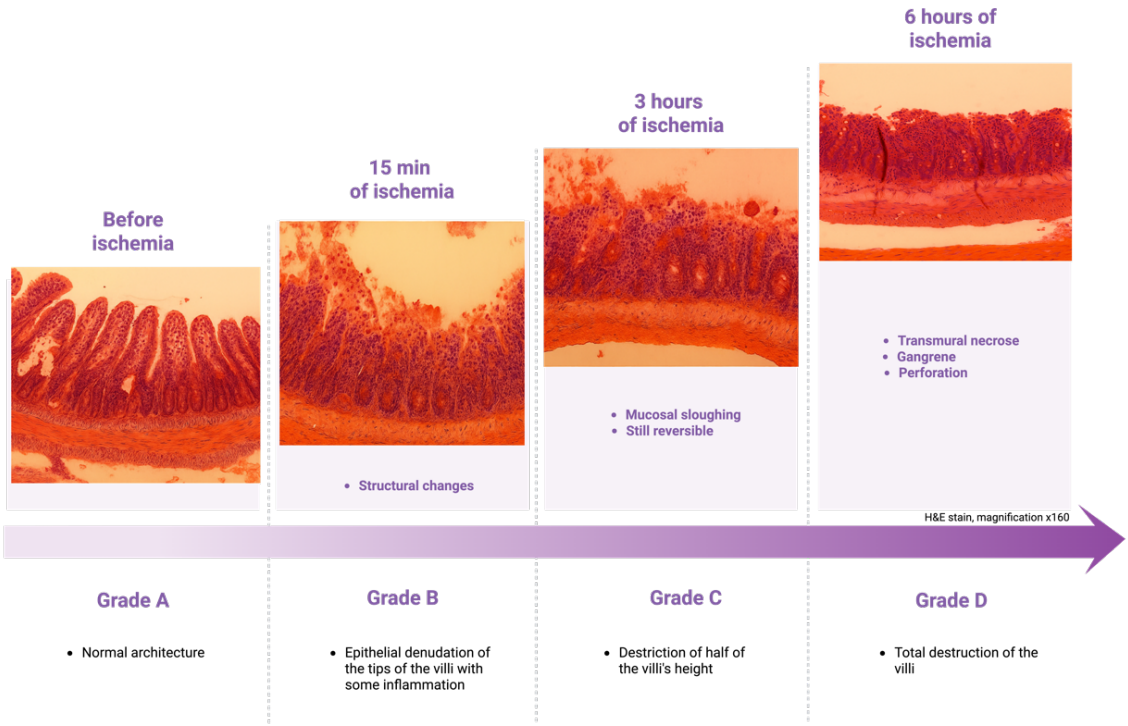

Figure 2. Histopathological changes of the intestine in absolute ischemia over time.

Legend: This figure shows the time-dependent histopathological changes that occur in the intestinal tissue during absolute ischemia. Structural changes in the intestinal villi occur after just 15 minutes. After 3 hours, mucosal exfoliation occurs, a condition that is potentially still reversible. After 6 hours, irreversible damage such as transmural necrosis, gangrene, and perforation develops. At this stage, clinical signs of peritonitis appear. The microscopic images illustrate the progressive tissue damage in the respective time intervals. The figure underlines the clinical relevance of early therapeutic intervention, as time plays a crucial role (source: Udassin R, et al. 1994, Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/ k04q76z).

The graphical representation in Figure 2 not only illustrates the pathophysiological sequence of intestinal ischemia but also serves as a visual decision-support tool in determining the timing and necessity for surgical resection.

2.4 Treatment

2.4.1 Volume and vasopressor management

Adequate volume substitution and optimization of cardiac output are essential therapeutic measures to maintain organ perfusion and prevent ischemic sequelae (Yuan, 2022; Garofalo M et al., 2002). For the treatment of non-occlusive mesenteric ischemia (NOMI), the use of vasodilators such as papaverine may be useful, as they cause a targeted improvement of mesenteric microcirculation (Yuan, 2022; Garofalo M et al., 2002).

2.4.2 Endovascular intervention

The therapeutic approach to mesenteric ischemia depends on the etiology as well as the clinical severity of the disease. Occlusive forms usually require surgery. In contrast, endovascular revascularization is becoming established as a first-line procedure in selected patients. Garzelli et al. (2024) were able to show that a persistent contrast medium flow on CT is a positive predictive marker for survival without intestinal resection. In contrast, Yu et al. (2024) pointed out that extensive bowel resection of more than 100 cm is associated with a significantly increased mortality rate. Angiography and selective intra-arterial application of vasodilators are increasingly considered promising additive therapy options for improving mesenteric blood flow (Sakamoto et al., 2020; Hasan et al., 2004).

2.4.3 Open surgery

Bowel resection

Surgical resection of non-viable sections of the intestine is a central therapeutic measure in mesenteric ischemia that is aimed at preventing the spread of necrotic processes and improving the prognosis of patients. The decision for resection is based on the extent of ischemic damage, the patient's general clinical condition, and the likelihood of functional regeneration of the intestine. Recent developments in diagnostic imaging and intraoperative assessment have significantly improved the treatment of this disease, although associated morbidity and mortality remain high.

Intestinal resection is indicated in particular if irreversible ischemic necrosis is detected. Predictive factors include organ failure, elevated lactate levels, and dilated intestinal loops in imaging (Nuzzo et al., 2018). The presence of peritonitis or hemodynamic instability is often an urgent indication for surgical rehabilitation (Kärkkäinen & Acosta, 2017). Early resection in the context of primary surgery is associated with an improved clinical course, while delayed intervention can significantly increase mortality (Matthaei et al., 2019).

Laparotomy is the standard procedure for surgical treatment, with the resection of necrotic sections of the intestine being the main goal (Petrov et al., 2024; Yuan, 2022). Early exploratory laparotomy is indicated in high-risk patients, especially due to the limited sensitivity of diagnostic procedures (Edwards et al., 2005; Abboud et al., 2008).

Despite the central role of surgical intestinal resection, early revascularization, especially by means of endovascular techniques, is increasingly becoming the focus of therapeutic strategies. The aim of these procedures is to restore mesenteric perfusion and thus avoid extensive intestinal resection. However, the success of these measures is highly dependent on timely diagnosis as well as on the underlying pathogenesis such as embolism or thrombosis (Kärkkäinen & Acosta, 2017; Srivastava et al., 2011). The increasing integration of advanced imaging techniques as well as interdisciplinary collaboration offer promising prospects for optimized care for this complex patient group.

Bowel transplantation

Intestinal transplantation is a life-saving option for patients with short bowel syndrome due to mesenteric ischemia. This severe disease, which is characterized by critically reduced perfusion of the intestine, can quickly lead to extensive necrosis and multi-organ failure if left untreated. Transplantation offers a therapeutic perspective, especially for patients with irreversible intestinal damage, although immunological complications and infection risks continue to pose considerable challenges. Advances in surgical technique, immunosuppression, and infection prevention have significantly improved the success rates of these procedures.

Intestinal transplantation is primarily indicated in patients with chronic intestinal failure due to mesenteric ischemia, especially when parenteral nutrition is no longer tolerated or poses significant risks (Pascher, 2024). Survival rates have improved significantly, with one- and three-year graft survival rates of about 80% and 70%, respectively, highlighting medical

advances in this area (Pascher, 2024). Nevertheless, these interventions are associated with high immunological requirements that require efficient immunosuppression to avoid rejection reactions (Pascher, 2024). Postoperative complications such as infections and malignancies require close monitoring and preventive measures (Pascher, 2024).

Despite the challenges involved, intestinal transplantation is an effective therapy for patients with advanced mesenteric ischemia. These procedures should be carried out in specialized centers that are proficient in surgical-technical skills as well as immunological and infectious disease aspects. The establishment of such multidisciplinary centers has been shown to contribute to improving patient care (Nuzzo et al., 2017; Nuzzo et al., 2018).

2.4.4 Prognostic factors

Numerous parameters are associated with an unfavorable prognosis in mesenteric ischemia. The extent of intestinal necrosis is one of the strongest predictors of mortality. Paladino et al. (2014) showed that necrosis of the right colon in combination with massive infestation of the small and large intestine is associated with high lethality. Intestinal perforation significantly worsens the prognosis, as it markedly increases the risk of septic complications and multi-organ failure (Dhamnaskar et al., 2016). The development of systemic organ dysfunction, especially acute renal or respiratory failure, is also associated with significantly increased mortality (Kumar et al., 2023; Wu et al., 2020).

2.5 Coagulation and coagulopathy

2.5.1 The role of the coagulation cascade

The coagulation cascade is a central element of hemostasis and enables the formation of a stable thrombus through a complex sequence of enzymatic reactions. This highly regulated biological system serves to maintain vascular integrity after injury and prevents excessive blood loss. The cascade is traditionally divided into an intrinsic and an extrinsic activation route, which finally converge into a common final route, the so-called “common” pathway. This leads to the formation of thrombin and consequently to the polymerization of fibrin. Stringent regulation of the coagulation cascade is essential to prevent uncontrolled activation that could otherwise

result in systemic thrombosis. In the following, the central components and mechanisms of coagulation are discussed in detail.

2.5.2 Intrinsic and extrinsic pathways

The intrinsic activation of coagulation begins with the contact of the blood with foreign surfaces. In this case, the prekallikrein system is activated, which successively activates coagulation factors XII, XI, and IX. In the further course, a multiprotein complex of factors IX, VIII, and X is formed, which catalyzes the conversion of factor X into its active form Xa in the presence of calcium ions (Blanco, 2017) (**Figure** 3).

In contrast, the extrinsic system is triggered by exposure to tissue factor (TF) in the context of vascular injury. The tissue factor forms a complex with factor VIIa, which also mediates the activation of factor X. This route is particularly important for the rapid onset of the coagulation reaction (Neuenschwander, 2006; Rao, 2006) (**Figure 3**).

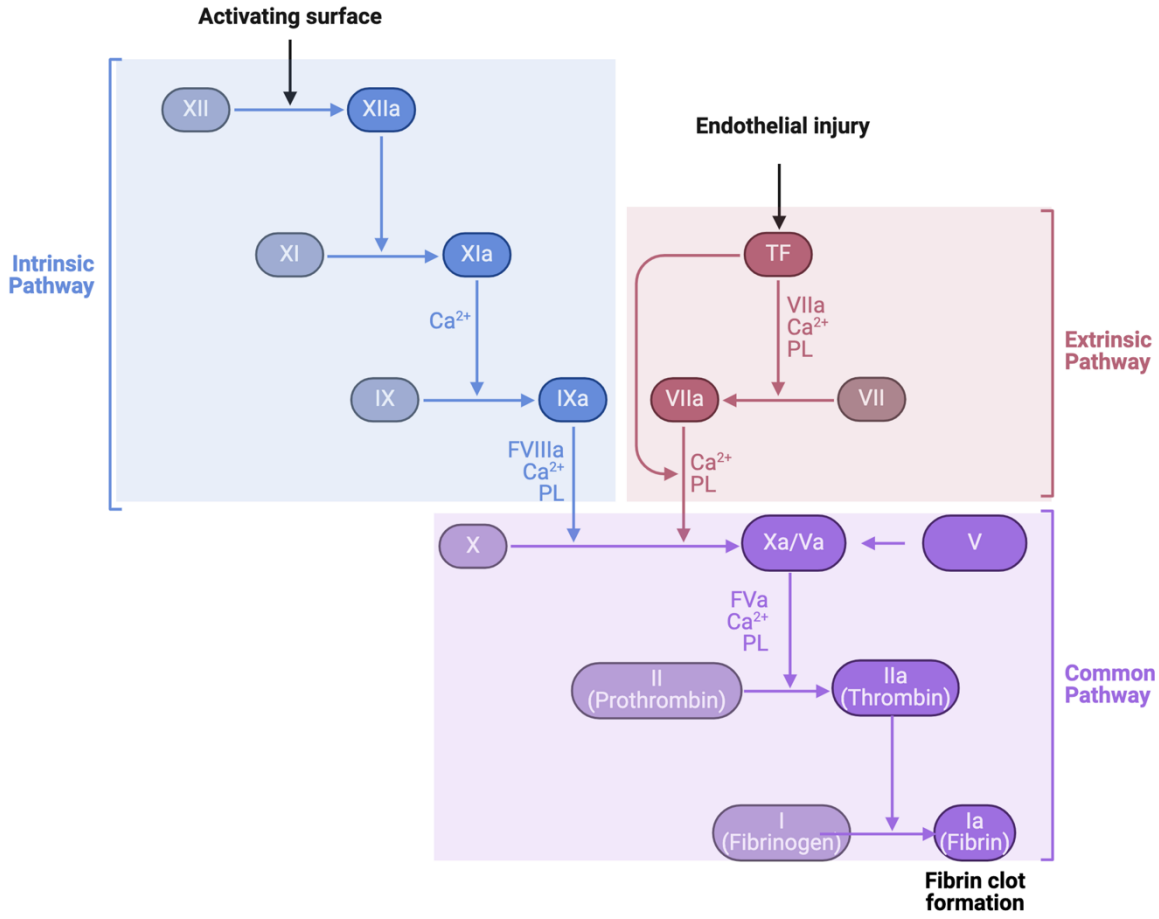

Figure 3. Schematic representation of the extrinsic, intrinsic, and common signaling pathways of blood clotting.

Legend: The figure shows the three main components of plasma blood clotting: the intrinsic (blue), the extrinsic (red), and the common (purple) pathways. The intrinsic cascade is triggered by contact with an activating surface and leads to the activation of factor X via factors XII, XI, and IX. The extrinsic pathway is initiated by endothelial injury, with the tissue factor (TF)-VIIa complex mediating direct activation of factor X. The color coding makes it easier to distinguish the paths and their respective factors. (Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/afek7yu)

Abbreviations: PL – phospholipids; Ca^{2+} – calcium ions; TF – tissue factor; F – Factor

2.5.3 Common pathway and thrombin generation

Both of these activation pathways result in the activation of factor X to Xa. This represents a central switching point of coagulation. In combination with the cofactor factor V, factor Xa catalyzes the conversion of prothrombin (factor II) to active thrombin (Núñez-Navarro et al., 2019) (**Figure 4**).

Thrombin is a multifunctional enzyme that not only converts fibrinogen into fibrin, but also activates a number of other coagulation factors and platelets. This positive feedback leads to the enhancement of the coagulation cascade and the stabilization of the thrombus (Blanco, 2017).

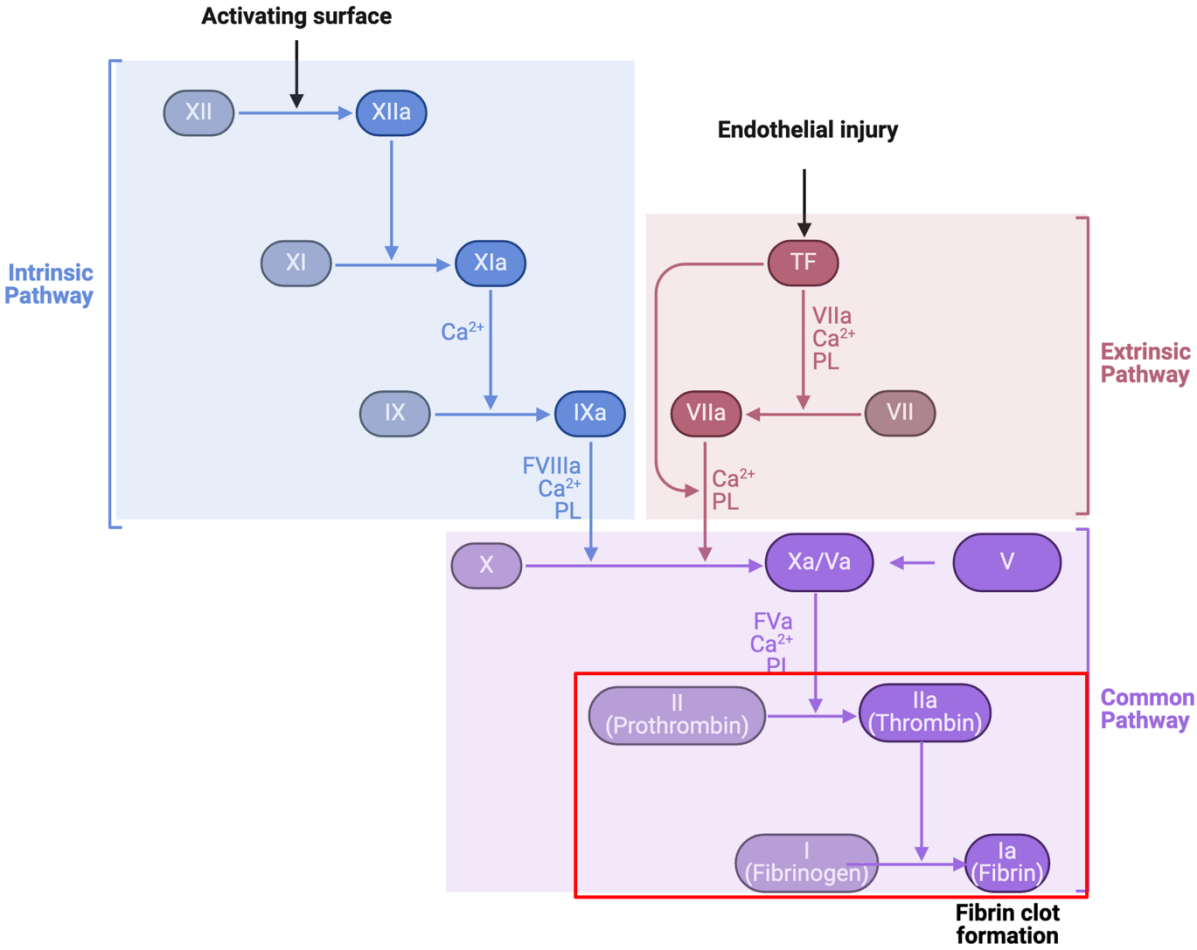

Figure 4. The common pathway of plasma coagulation (common pathway).

Legend: This figure highlights the common pathway (purple, outlined in red) of the coagulation cascade, where both the intrinsic and extrinsic signaling pathways converge. Central to this is the activation of factor X to Xa, which, together with factor Va, calcium, and phospholipids, catalyzes the conversion of prothrombin (factor II) to thrombin (factor IIa). Thrombin then cleaves fibrinogen (factor I) to fibrin (factor Ia), which forms the basis for the formation of a stable fibrin thrombus. The common pathway thus represents the final step towards effective hemostasis. (Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/afek7yu)

Abbreviations: PL – phospholipids; Ca^{2+} – calcium ions; TF – tissue factor; F – Factor

2.5.4 Regulation and localization

The precision and localization of the coagulation reactions are controlled by numerous endogenous inhibitors. These include the tissue factor pathway inhibitor (TFPI), the protein C/protein S system, and antithrombin. These components prevent systemic coagulation from spreading and limit reactions to the site of vascular injury (Moerloose & Boehlen, 2008). The targeted localization of the coagulation processes is also supported by the binding of the coagulation factors to phospholipid membranes of cells. This membrane-associated attachment

accelerates the enzymatic reactions and promotes their spatial limitation (Kovalenko & Panteleev, 2024).

2.5.5 Clinical implications and therapeutic targets

A sound understanding of the coagulation cascade is of great clinical relevance, especially in the treatment of thromboembolic diseases such as coronary heart disease or acute lung damage. Anticoagulative therapies, including unfractionated heparin and low-molecular heparins, specifically intervene in the cascade to prevent thrombotic complications (Langer & Gawaz, 2005). Factor Xa represents an important therapeutic target due to its central function in thrombin formation. The development of specific Xa inhibitors is aimed at effective anticoagulation with a reduced rate of side effects (Núñez-Navarro et al., 2019).

Although the classical cascade model of coagulation provides valuable insights, it shows weaknesses in certain clinical scenarios. For example, patients with hemophilia may show bleeding tendencies despite an intact extrinsic system. A cell-based coagulation model that highlights the role of cellular surfaces in the regulation and localization of coagulation processes provides a more realistic representation of hemostasis in vivo (Hoffman, 2003). This concept illustrates the high complexity of coagulation and the need for finely tuned regulation to maintain vascular homeostasis and avoid pathological thrombosis.

2.6. Hypercoagulability

The term hypercoagulability describes a pathophysiological condition in which the hemostatic balance of the blood is shifted in favor of an excessive tendency to clot. This leads to an increased tendency to thrombosis and represents a relevant clinical problem, as both venous and arterial thromboembolic complications are associated with significantly increased morbidity and mortality. The etiology can be either hereditary or acquired, with a variety of molecular mechanisms causally involved. In the following sections, the pathophysiological basis, predisposing factors, and diagnostic and therapeutic strategies for hypercoagulability are presented.

2.6.1 Mechanisms of hypercoagulability

The development of hypercoagulability is due to an imbalance within the coagulation system in which procoagulant factors outweigh anticoagulant mechanisms and thus promote excessive

thrombus formation (Ralph et al., 2023; Perler, 1995). Hereditary forms of hypercoagulability are often genetic defects, such as the factor V Leiden mutation or congenital deficiencies of natural anticoagulants such as protein C, protein S, or antithrombin (Hussain et al., 2022; Thomas & Roberts, 1997). Acquired forms of hypercoagulability can occur, among other things, in the context of malignancies in which tumor-associated factors disrupt the coagulation balance. Drug influences, such as hormonal contraceptives or chemotherapeutic agents, can also significantly increase the thrombotic risk (Nasser et al., 2020).

2.6.2 Risk factors and clinical implications

Hypercoagulability is a significant risk factor for the occurrence of venous thromboembolism (VTE) and arterial occlusion. The effect is more pronounced than in myocardial infarctions, especially with regard to ischemic strokes (Maino et al., 2015). The most important risk factors include genetic dispositions, malignant underlying diseases, chronic inflammatory processes, and certain lifestyle factors. For example, dehydration and increased salt consumption can contribute to the development of thrombosis via increased secretion of the von Willebrand factor (Dmitrieva & Burg, 2014). The clinical presentation is diverse and ranges from asymptomatic constellations to fulminant thrombotic events with a potentially lethal course. This makes individual risk stratification and targeted management indispensable (Shah et al., 2021).

2.6.3 Diagnosis and management

The diagnosis of hypercoagulability requires the use of special laboratory chemical analyses to detect coagulation abnormalities and, if necessary, molecular genetic testing for known thrombophilic mutations (Hassouna, 2009; Perler, 1995).

Thrombin generation analysis

Thrombin generation analysis (TGA) is a comprehensive hemostaseological procedure that evaluates the ability of plasma to form thrombin. Thrombin is a central enzyme in the coagulation cascade, and its generation reflects the balance between procoagulant and anticoagulant mechanisms. Due to these properties, TGA is a highly informative test for estimating bleeding and thrombosis tendencies in different clinical settings. It offers added value especially in situations where conventional coagulation tests are not sufficiently sensitive or specific, such as when monitoring new therapies for hemophilia, autoimmune diseases, or

pregnant women with hereditary thrombophilia. The following outlines the clinical areas of application, advantages, and limitations of TGA.

TGA is used to assess thrombin formation in patients being evaluated for thrombophilia. It enables a global assessment of the hemostatic balance and provides valuable information in the case of unexplained bleeding tendencies for which standard tests do not allow a clear statement (Okhrem et al., 2024; Konkolewski et al., 2024). In patients with hemophilia, TGA is used to monitor non-factor-based therapeutic approaches that work by increasing thrombin formation. This monitoring is essential, as excessive thrombin formation increases the risk of thrombosis (Josset et al., 2024).

TGA is also used to evaluate hypercoagulability in autoimmune diseases such as antiphospholipid syndrome or systemic lupus erythematosus. Here, thrombin formation correlates with disease activity and helps to assess the risk of thromboembolic events (Billoir et al., 2021).

In the context of pregnancy, TGA allows an adequate determination of the physiological change towards hypercoagulability. It supports the detection of coagulation defects and helps control hereditary thrombophilia (Luterán et al., 2024).

TGA enables a detailed analysis of the coagulation system by quantifying the initiation, propagation, and inhibition of thrombin formation. As a result, it provides a more comprehensive picture than classic coagulation tests, which only measure isolated coagulation factors (Lebreton & Mandorfer, 2024; Roshal, 2013). The development of standardized and automated systems such as the ST Genesia has facilitated the integration of TGA into the clinical routine. These systems enable consistent quality and reproducibility of measurement results (Okhrem et al., 2024; Luterán et al., 2024).

TGA can be used in clinical research as well as in routine care. Its use ranges from drug monitoring to the safety testing of pharmaceutical substances, for example in the development of immunoglobulin preparations (Parunov et al., 2021).

Despite the promising potential of TGA, its routine clinical application has thus far been limited. A major reason for this is the still existing need for comprehensive validation as well as the lack of standardization of the method (Salvagno & Berntorp, 2017).

In summary, it can be stated that TGA allows an extremely differentiated assessment of hemostasis and thus represents a valuable instrument for the global evaluation of the coagulation balance. Especially in selected clinical situations, such as the monitoring of innovative therapies for the treatment of hemophilia or the risk stratification of thrombotic events in the context of autoimmune diseases, the method proves to be clinically relevant and meaningful.

Nevertheless, there are still substantial challenges with regard to the standardization of measurement methods and the interpretation of the data obtained. These limitations need to be addressed in a targeted manner in future studies and consensus processes in order to harness the full diagnostic and prognostic potential of TGA in everyday clinical practice.

Key parameters and clinical significance of TGA

In contrast to conventional coagulation tests, TGA allows a comprehensive assessment of the hemostatic system by simultaneously imaging both procoagulant and anticoagulant activities. The analysis focuses on four central parameters: lag time, time-to-peak, peak thrombin, and endogenous thrombin potential (**Figure 5**). These parameters have a high clinical relevance in the differentiation of various coagulopathies, such as those that occur in COVID-19, disseminated intravascular coagulation (DIC) or sickle cell disease. The individual parameters and their clinical implications are presented in detail below.

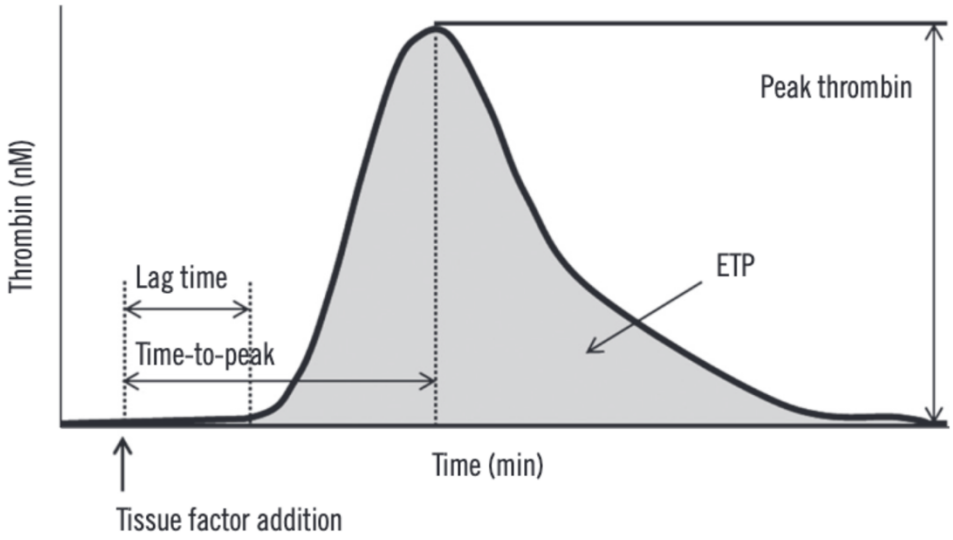

Figure 5. Parameters of thrombin formation analysis.

Legend: By adding tissue factor, thrombin is formed in the course of the reaction, which is reflected in a bell-shaped thrombin formation curve. The lag time refers to the time at which one sixth of the maximum thrombin level is reached. The time-to-peak describes the time when the maximum amount of thrombin is reached (peak thrombin). Endogenous thrombin potency (ETP) corresponds to the area under the thrombin formation curve and represents the total amount of thrombin formed over time. (Source: Kim et al., 2015)

Lag Time: The lag time describes the period of time that elapses until the initial thrombin formation. A prolonged lag time suggests a hypocoagulable state, such as that observed in patients with COVID-19. Here, it indicates a limited thrombin formation capacity as well as possible consumption coagulopathy (Tiscia et al., 2024). In the context of DIC, lag time is related to the concentration of protein C and acts as an independent prognostic marker (Lee et al., 2014).

Time-to-Peak: This parameter records the time it takes to reach the maximum concentration of thrombin. Prolonged time-to-peak is typical of hypocoagulable states such as those seen in DIC and COVID-19, as delayed thrombin formation negatively affects coagulation dynamics (Tiscia et al., 2024; Lee et al., 2014). In contrast, sickle cell anemia shows a shortened time-to-peak, indicating a hypercoagulable constellation (Feugray et al., 2022).

Peak Thrombin: The maximum concentration of thrombin formed reflects the potential for coagulation activation. Reduced peak thrombin levels are documented in hypocoagulable conditions such as COVID-19 and after cardiac surgery (Tiscia et al., 2024; Ericksen et al.,

2022). Increased peak values in sickle cell disease, on the other hand, indicate an increased risk of thrombosis and are predictive of vaso-occlusive crises (Feugray et al., 2022).

Endogenous thrombin potential (ETP): The ETP records the cumulative amount of thrombin generated over a defined period of time and thus reflects the total coagulation potential. A reduction in ETP is observed in hypocoagulable conditions such as DIC and after cardiac surgery (Lee et al., 2014; Ericksen et al., 2022). Interestingly, the ETP remains unchanged in patients with sickle cell disease despite other evidence of hypercoagulability (Feugray et al., 2022).

Biological variability and standardization problems

The TGA parameters are subject to pronounced intra- and interindividual variability. This variability significantly influences the interpretation of the measurement results (Mairesse et al., 2021; Melnichkova et al., 2024). The so-called "Index of Individuality" and the "Reference Change Value" are essential for correctly classifying follow-up studies and defining analytical quality criteria (Mairesse et al., 2021; Melnichnikova et al., 2023). The lack of standardization in terms of test conditions, reagents, and reference intervals is a major obstacle to the broad adoption of TGA in clinical practice (Mairesse et al., 2021; Melnichnikova et al., 2023).

Clinical significance and areas of application

In COVID-19, TGA shows a hypocoagulable pattern and contributes significantly to the understanding of COVID-associated coagulopathy (Tiscia et al., 2024). The TGA parameters correlate with the severity of the DIC and provide valuable prognostic information (Lee et al., 2014). TGA allows the identification of hypercoagulability, with specific parameters prognostically relevant for vaso-occlusive events (Feugray et al., 2022).

Postoperative thrombin formation profiles differ significantly between cardiac surgery and non-cardiac surgery procedures and influence individual therapy planning (Ericksen et al., 2022). **Figure 6** illustrates these differences using the thrombin genesis curves and depicts the dynamic changes in hemostatic balance after various surgical interventions.

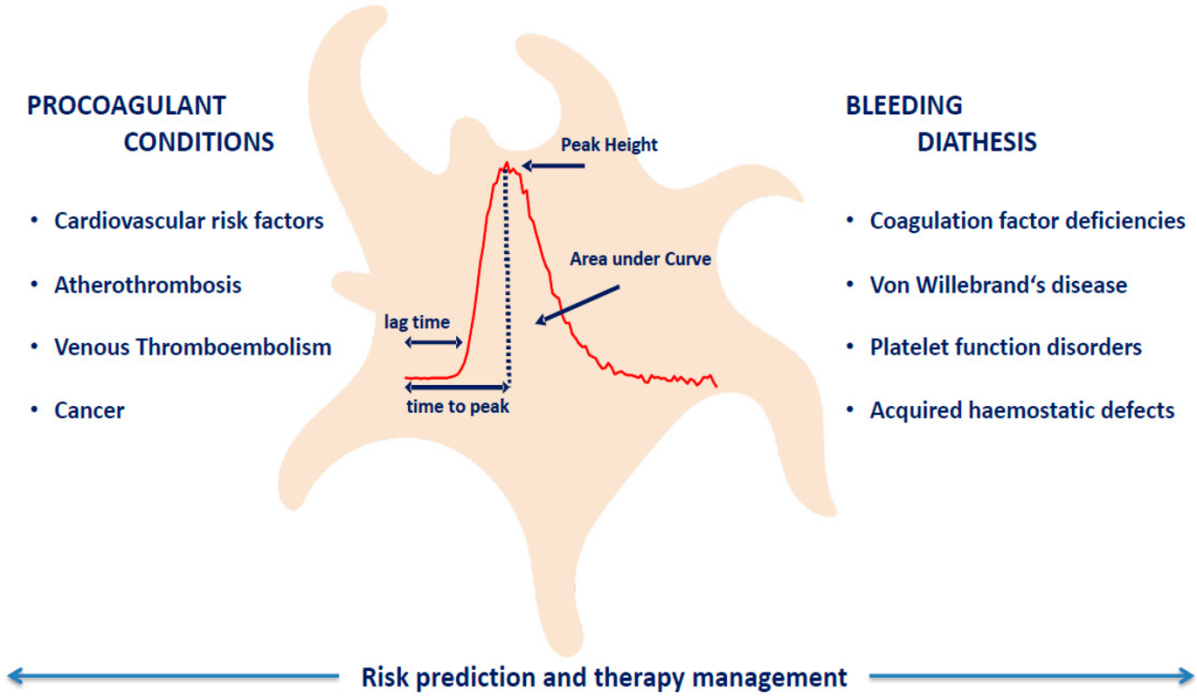

Figure 6. Thrombin generation curve: Clinical relevance for risk assessment and therapy control.

Legend: The figure shows the central role of thrombin generation analysis (TGA) in the clinical diagnosis and risk assessment of hemostatic disorders. The red curve represents thrombin generation over time. Important parameters such as lag time, time-to-peak, peak height, and the area under the curve (AUC) provide information about the balance between procoagulant and bleeding-associated states. On the left, procoagulant conditions are shown, including cardiovascular risk factors, atherothrombosis, venous thromboembolism, and malignancies. On the right, clinical situations with an increased risk of bleeding are shown, such as coagulation factor deficiencies, von Willebrand syndrome, platelet dysfunction, and acquired hemostatic defects. The thrombin generation curve thus allows a differentiated assessment of hemostatic capacity and supports individualized risk assessment as well as therapy management for both thrombotic and hemorrhagic clinical scenarios. (Source: Panova-Noeva et al., 2019)

Although TGA provides in-depth insights into the dynamics of the coagulation system, its clinical application is currently still limited by the need for further standardization and high biological variability. However, future research and the development of uniform test protocols could significantly promote the establishment of TGA as a component of precision medicine diagnostics and therapy optimization in different clinical contexts.

Therapeutic management

Therapeutic management includes the administration of anticoagulants such as heparins or vitamin K antagonists, the use of antiplatelet agents, and targeted lifestyle interventions to

reduce the thrombotic risk. In particularly high-risk situations, such as the perioperative period, the use of prophylactic anticoagulation is indicated (Kitrell & Berkwitt, 2012).

Although hypercoagulability is considered an established risk factor for thromboembolic events, it should be emphasized that not all affected individuals actually develop thrombosis. The interplay of multiple risk factors as well as exogenous influencing variables has a considerable impact on the individual risk situation. This underlines the relevance of personalized risk assessment and tailored treatment decisions (Hussain et al., 2022).

The scientific understanding of hypercoagulability is constantly evolving. In particular, research into molecular mechanisms and new therapeutic targets will help to make the management of this complex coagulation disorder even more effective and individualized in the future.

2.7 Mesenteric ischemia and hypercoagulability

The connection between hypercoagulability and the occurrence of mesenteric ischemia shortly after heart surgery can be traced back to a complex interplay of physical adaptation processes and consequences of surgery-related stress. Although mesenteric ischemia is rare, it is one of the dreaded complications after cardiac surgery and is often associated with high mortality.

Hypercoagulability is a pathologically increased thrombin formation that can trigger uncontrolled fibrin deposits or increased platelet aggregation (**Figure 7**). Due to the formation of microthromboemboli in the intestinal vessels, overactivity of the coagulation system can restrict blood flow to the intestine to such an extent that tissue damage occurs. In order to avoid consequential damage, rapid detection and targeted treatment are crucial.

As studies by Eris and colleagues (2013) show, both the physical stress response during surgery and the use of the heart-lung machine can further increase the clotting tendency. However, current data suggest that early anticoagulant therapy could improve patients' prognosis (Acosta-Mérida et al., 2023).

Thus far, it is unclear whether an increased potential for thrombin formation increases the risk of vascular complications in mesenteric ischemia after cardiac surgery. In order to measure this potential, so-called thrombin formation tests (carried out *in vitro* or *ex vivo*) are used, the reliability of which has already been confirmed in several studies (Davie 2006, Mann 2003).

Conventional coagulation tests often do not adequately capture the actual risk of thrombosis in mesenteric ischemia, which is why these special assays play a key role in such situations.

In order to estimate thrombin activity directly in the body, the prothrombin fragment F1+2 – a degradation product produced during the conversion of prothrombin to thrombin – is often analyzed (Capecchi 2021, Ota 2008). Thrombin-antithrombin complexes (TAT), which form when thrombin is neutralized by antithrombin (**Figure 7**), are also significant.

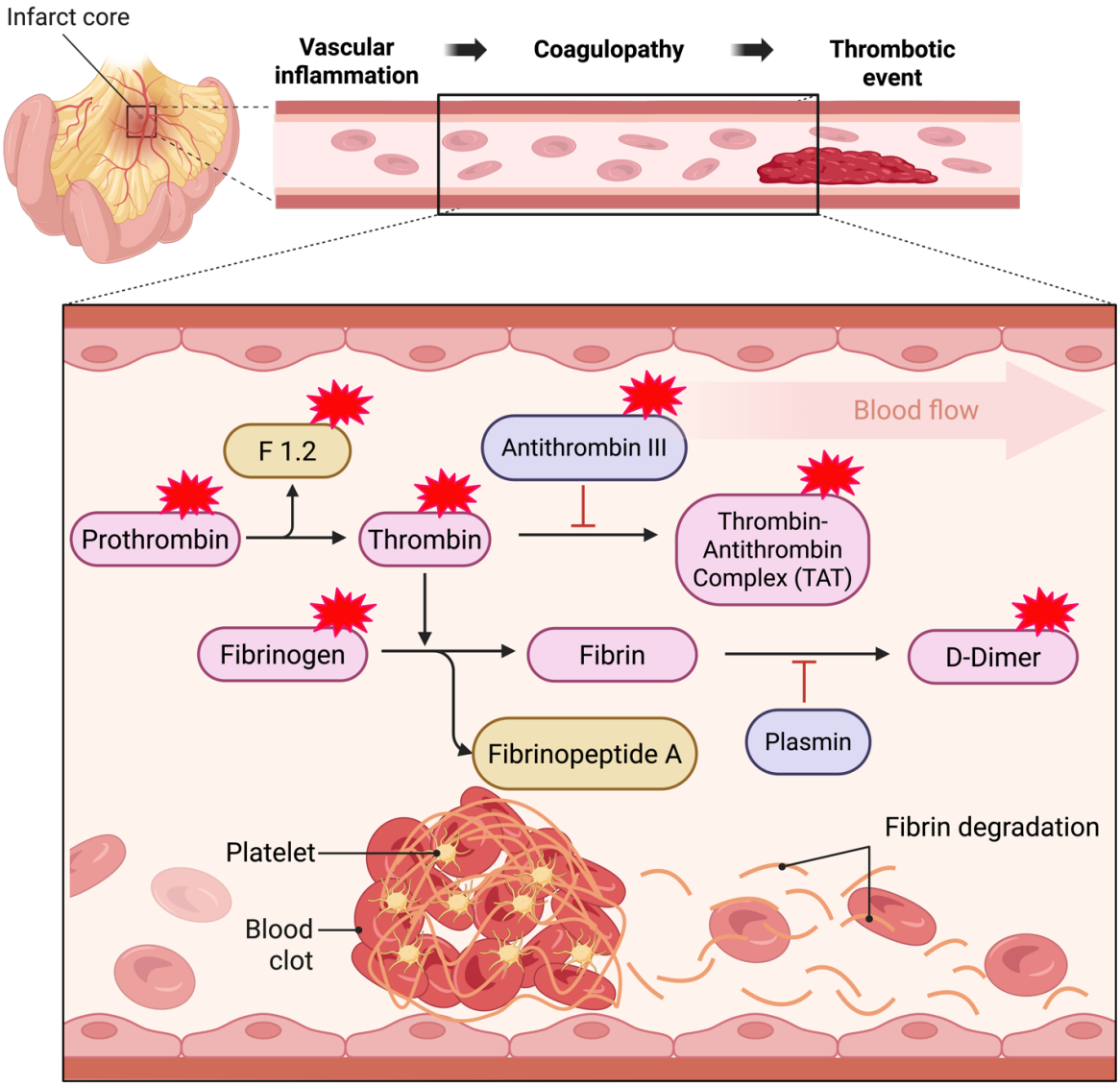

Figure 7. Coagulopathy at the site of mesenteric ischemia.

Legend: Pathophysiological relationship between vascular inflammation, coagulopathy, and thrombotic events. A vascular inflammatory reaction initiates coagulopathy with increased activation of the coagulation cascade. The conversion of prothrombin to thrombin leads to an increased formation of fibrin from fibrinogen, accompanied by a release of fibrinopeptide A. At the same time, an increased level thrombin-antithrombin complex (TAT) develops. The resulting fibrin thrombus is stabilized by platelet aggregation and can lead to vascular occlusion. The fibrinolytic system breaks down fibrin into D-dimers, which can thus serve as biomarkers for thrombotic events. (Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/yu3yu52)

2.8 Aims of this work

The present study investigated the extent to which hypercoagulability after cardiac surgery is related to mesenteric ischemia and how this coagulation disorder affects thrombin formation.

3. Material and methods

3.1 Cohort

Ethics statement

The study was approved by the Ethics Committee of Justus Liebig University Giessen – Local Registration Number: GI AZ 293/20, Amendment 2 (12.08.2022) and has a unique identifier on www.clinicaltrials.gov: NCT06365827. All participants gave their written consent to participate in this prospective registry study.

Screening and patient cohort

This prospective observational study included 500 out of 929 consecutive patients who underwent open-heart surgery at a clinic between March 2022 and December 2023. Patients with chronic organ insufficiency, preoperative infections (e.g., endocarditis), severe immunodeficiency, or lack of consent were excluded.

Target population

Of 500 consecutive patients, 6 (1.2%) showed confirmed mesenteric ischemia. One patient was excluded from the analysis due to non-occlusive mesenteric ischemia (NOMI) diagnosed early after admission to the intensive care unit and was treated with prostaglandin perfusion. Retrospectively, 25 of 101 high-risk patients with hyperinflammatory status (IL-6 >600 ng/l)

and metabolic acidosis (lactate >4 mmol/l) were assigned to a mesenteric ischemia group (n=5) or a control group (n=20) in a ratio of 1:4. The study population was thus divided into two groups: mesenteric ischemia (Me-Is) and controls (**Figure 8**).

Figure 8. Overview of the total population and the target population.

(Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/mua27x1)

3.2 Clinical data collection

Medical data was recorded and evaluated electronically using Research Electronic Data Capture (REDCap) (department internal server, administrator: Zulfugar Taghiyev). The prediction models used comply with the TRIPOD guidelines (TRIPOD+AI) (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines) (Collins et al. (2015).

3.3 Laboratory storage

The aliquots obtained were stored at −80 °C in a temperature-controlled ultra-low temperature freezer in 81 cryoboxes according to an established standard procedure and were systematically recorded according to the respective sample number. The established biobank met the quality requirements of ISO 21899:2020 (International Organization for Standardization) (2020) online). This standardized and documented storage ensured sample stability and traceability for all further analyses.

3.4. Laboratory analysis

Collection of samples and laboratory measurements of I-FABP

Blood samples were taken at five time point perioperatively according to the following sampling plan: T_0 – preoperative baseline samples; T_1 – intraoperatively, after the end of ECC and protamine administration; T_2 – postoperatively, at admission to the intensive care unit (ICU); T_3 – 12 hours after ICU admission; T_4 – 36 hours after ICU admission. **Figure 9** shows an overview of the sampling plan.

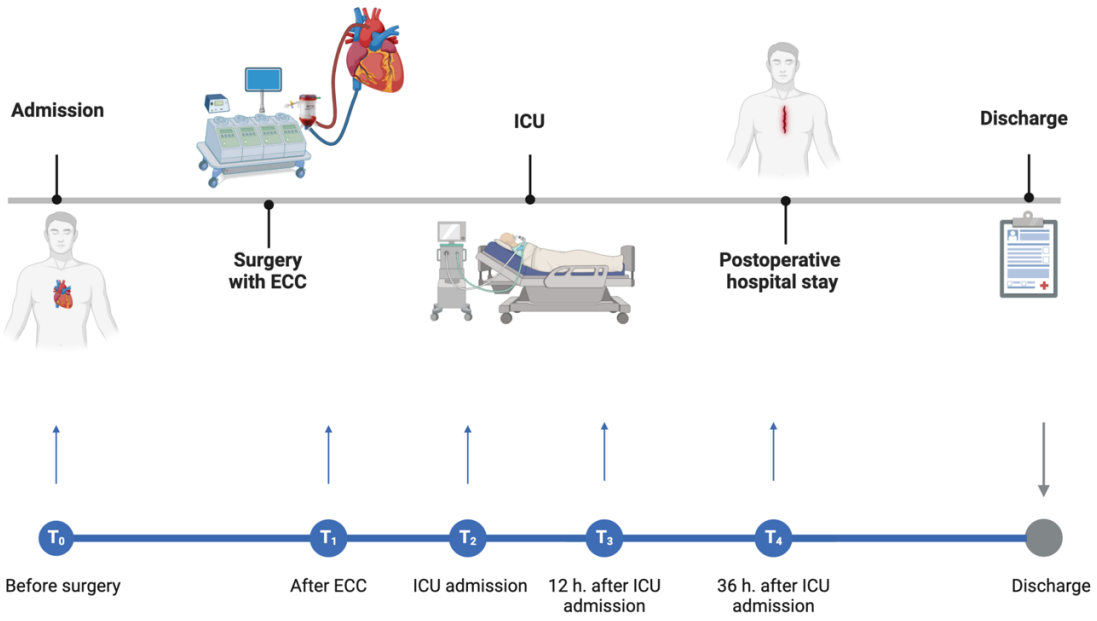

Figure 9. Overview of sampling time points.

Legend: T_0 before surgery; T_1 after protamine administration (after ECC); T_2 at ICU admission; T_3 12 hours after ICU admission; T_4 36 hours after ICU admission. (Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/3i7yjb0)

Each blood sample was collected simultaneously with samples collected for regular perioperative laboratory tests. The samples were centrifuged within 30 min of collection (at 3000 rpm for 10 min at 4˚C), and a 500-µL aliquot was stored at -80°C until analysis was carried out at the Clinical Research Center laboratory at the University of Marburg. I-FABP levels in serum samples were determined using ELISA (high-sensitivity immunoassay kit from Hycult®Biotech (HK406); Hycult Biotechnology B.V., Uden, The Netherlands). The measurement of human I-FABP is feasible within the range of 47 to 3000 pg/ml. In cases where samples exceeded 3000 pg/ml, samples were diluted up to tenfold with a buffer solution in

accordance with the manufacturer's instructions. Levels of lactate and IL-6 were measured in an in-house accredited clinical laboratory using certified and standardized protocols.

Collection of samples and laboratory measurements of coagulation state

Sampling and laboratory measurements of the citrate blood samples were taken perioperatively at 3 time points: T0 – preoperatively; T1 – if admitted to the intensive care unit (ICU); T2 – 12 hours after ICU admission; An overview is shown in **Figure 10**.

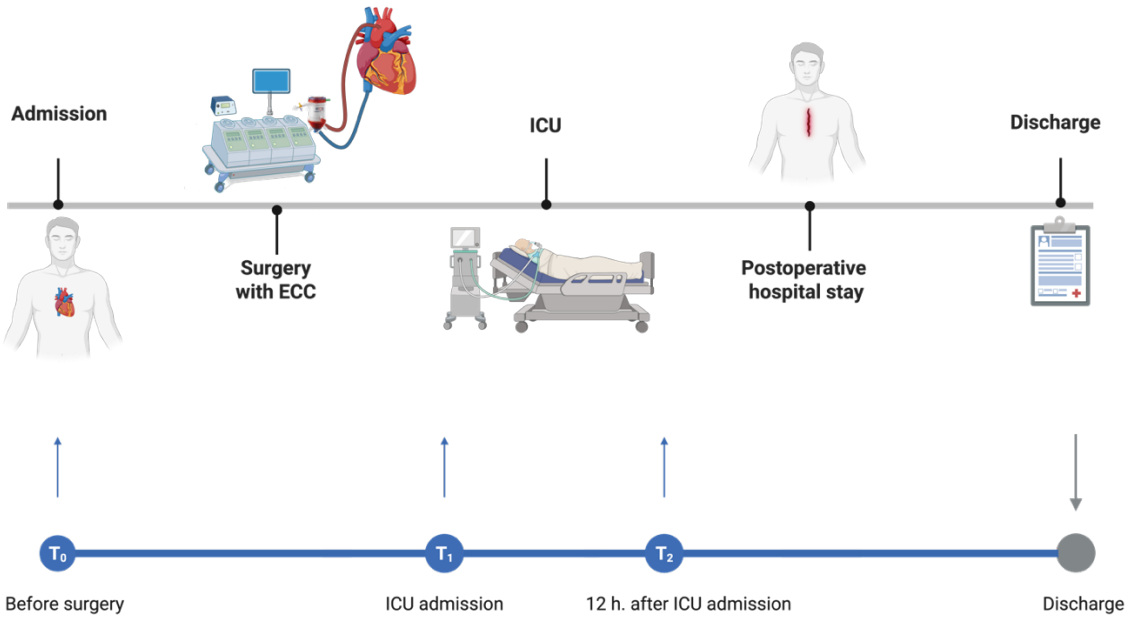

Figure 10. Overview of sampling time points of citrate blood samples.

Legend: T_0 before surgery; T_1 at ICU admission; T_2 12 hours after ICU admission. (Created in BioRender. Taghiyev, T. (2025) https://BioRender.com/ivgeuwc)

Blood was collected in citrate-containing tubes and centrifuged twice (2000 × g, 10 min, at room temperature) to obtain platelet-poor plasma (PPP). Plasma was carefully removed, aliquoted, and immediately stored at -80°C. Before analysis, rapid thawing (37°C water bath), careful mixing, and storage at 4°C until examination (maximum 2 hours after thawing) was carried out.

For quality control, visual assessments of the platelet-free supernatant were made after each centrifugation step. The samples were immediately frozen to protect labile biomarkers. Polypropylene tubes were used to minimize adsorption.

For the quantitative determination of the prothrombin fragment F1+2 in human plasma, the Enzygnost™ F1+2 (monoclonal) assay from Siemens Healthineers (Marburg, Germany) was used. This enzyme immunological test is used to diagnose, monitor, and evaluate acquired or hereditary blood clotting disorders and supports the risk assessment for thrombosis and the monitoring of the effectiveness of anticoagulants.

The concentrations of the thrombin-antithrombin complexes (TAT) were determined using the Enzygnost™ TAT micro assay from Siemens Healthineers. This ELISA test enables the quantitative determination of TAT complexes in plasma and is used to diagnose hypercoagulability conditions, such as disseminated intravascular coagulopathy (DIC).

Thrombin formation was analyzed with the RC Low reagents on the Ceveron® s100 system of the Technoclone (Vienna, Austria). The Ceveron® s100 is a fully automated coagulation analyzer designed to perform coagulation, chromogenic, and turbidimetric assays as well as thrombin generation testing (TGA) and quenching assays. The RC Low reagents have been specially developed for the investigation of thrombophilic tendencies and enable a detailed analysis of thrombin formation.

3.5 Statistical analysis

The statistical analyses were conducted utilizing Statistical Package for the Social Sciences (SPSS®) version 27.0 for Mac OS (IBM® Corporation released 2019, Armonk, New York, United States) and GraphPad Prism version 9.0.0 for Mac OS (GraphPad Software released 2020, San Diego, California USA) following appropriate coding procedures. Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are presented as frequencies and percentages. Inter-group disparities across various time points were assessed employing one-way analysis of variance (ANOVA), with Tukey's post hoc test being applied in instances of observed differences. The normality of data distribution within each group was evaluated using the Shapiro-Wilk test. For normally distributed variables, Student's t-test (unpaired) was utilized for comparison, and non-normally distributed variables were subjected to analysis using either the Mann-Whitney U-test or the Wilcoxon-signed-rank test.

Comparisons between different groups were made employing Pearson's chi-squared test or Fisher's exact test to ascertain independence of measurements. A standard confidence level of

95% was set, and statistical significance was determined at a p-value less than 0.05 (two-tailed). In instances of multiple comparisons, adjustments were made utilizing the Bonferroni correction method.

For propensity score matching, perioperative risk variables including age, body mass index (BMI), sex, EuroSCORE II, platelet count, partial thromboplastin time (PTT), and interleukin-6 (IL-6) and lactate levels were used to compare the two groups and minimize selection bias. Matching was performed at a 1:4 ratio (5 mesenteric ischemia patients vs. 20 control patients) based on propensity scores, without replacement.

4. Results

4.1 Procoagulant state

4.1.1 Hypercoagulopathy during mesenteric ischemia

The initial characteristics of the total population (n = 500) and the target population (n = 25) are shown in **Table 1**. In the target group, the proportion of female patients was higher (36%) compared to the overall group (26%), but this was without statistical significance (p = 0.291). On average, the target population was significantly older than the overall population (69.80 ± 5.95 vs. 53.50 ± 26.72 years; p = 0.003). A higher prevalence of heart failure NYHA class III–IV was also observed in the target group (64% vs. 30%; p < 0.001). Patients in the target population also showed a significantly lower glomerular filtration rate (eGFR) (74.5 ± 27.1 vs. 84.8 ± 26.0 ml/min/1.73 m²; p = 0.001) and a significantly higher EuroSCORE II (10.92 ± 9.9 vs. 4.06 ± 3.6; p = 0.001). Other variables did not differ significantly between the two groups.

Table 1. Baseline characteristics of total and target population.

Variable, n (%) or mean ±SD	Total Population (n=500)	Target Population (n=25)	p Value
Female, n (%)	132 (26)	9 (36)	0.291
BMI, kg/m²	28.11 ± 5.05	29.25 ± 5.45	0.273
Age, y	53.50 ± 26.72	69.80 ± 5.95	0.003
COPD Gold III-IV, n (%)	22 (4.4)	2 (8)	0.400
NYHA class III- IV, n (%)	152 (30)	16 (64)	0.000
CCS class III-IV, n (%)	66 (13.2)	4 (16)	0.688
Diabetes on insulin, n (%)	46 (9.2)	5 (20)	0.075
HbA1c, %	5.98 ± 0.95	6.07 ± 0.78	0.642
Ejection fraction, %	53.3 ± 11.14	50.2 ± 10.65	0.174
Serum creatinine, mg/dl	1.0 ± 0.6	1.2 ± 1.2	0.128
eGFR, ml/min/1.73 m² *	84.8 ± 26.0	74.5 ± 27.1	0.001

STS-Prom score, predicted mortality, %	5.29 ± 7.22	6.85 ± 7.95	0.295
EuroSCORE II	4.06 ± 3.6	10.92 ± 9.9	0.001

*Cockcroft-Gault Equation (Cockcroft et al., 1976).

Abbreviations: BMI=Body Mass Index; COPD GOLD=Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease Stages; NYHA=New York Heart Association Functional Classification; CCS=Canadian Cardiovascular Society Angina Grading Scale; HbA1c=Glycated Hemoglobin; eGFR=Estimated Glomerular Filtration Rate; STS-PROM Score=Society of Thoracic Surgeons Predicted Risk of Mortality; EuroSCORE II =European System for Cardiac Operative Risk Evaluation II.

After adjusting the baseline variables by propensity score matching, there were no significant differences between the mesenteric ischemia group (Me-Is; n = 5) and the control group (Non Me-Is; n = 20) (**Table 2**). Preoperative features were comparable between the two groups. Intraoperatively, the two groups also did not differ significantly in terms of combined procedures, duration of extracorporeal circulation (CPB time), and duration of aortic clamping time. Postoperatively, there tended to be a higher frequency of the need for mechanical support systems in the Me-Is group compared to the control group (60% vs. 25%; p = 0.134), but this difference was not significant (**Table 2**).

Table 2. Baseline characteristics of propensity matched population.

Variable, n (%) or mean ±SD	Me-Is (n=5)	Non Me-Is (n=20)	p Value
Preoperative characteristics			
Male, n (%)	4 (80)	11 (55)	0.307
BMI, kg/m^2	28.2 ± 6.2	30.3 ± 4.7	0.455
Age, y	68.7 ± 4.3	70.8 ± 7,6	0.324
Ejection fraction, %	51.7 ± 10.4	48.6 ± 10.9	0.589
STS-Prom score, predicted mortality, %	6.5 ± 6.8	7.2 ± 9.1	0.874
EuroSCORE II	11.5 ± 10.4	10.5 ± 9.3	0.835
eGFR, mL/min/1.73 m^2 *	76.1 ± 27.2	72.9 ± 26.9	0.814

HbA1c, %	5.7 ± 1.4	6.1 ± 0.7	0.360
Intraoperative characteristics			
Combined surgery, n (%)	2 (40)	11 (55)	0.548
CPB time, mean ± SD, hh: mm	2:39 ± 0:43	3:18 ± 0:50	0.626
Cross-clamp time, mean ± SD, hh: mm	1:30 ± 0:30	1:29 ± 0:35	0.871
Postoperative characteristics			
Need for assist devices (n, %)	3 (60)	5 (25)	0.134
ICU stay, days	5.6 ± 6.2	8.7 ± 8.5	0.455
Invasive ventilation, h	39.2 ± 28.1	61.2 ± 89.6	0.598
Dialysis, n (%)	1 (20)	4 (20)	1.000
Re-thoracotomy, n (%)	2 (40)	2 (10)	0.102
APACHE II score	23.7 ± 7.6	22.9 ± 3.3	0.717
SOFA score	9.0 ± 2.7	8.4 ± 2.6	0.651
Norepinephrine support, µg/kg	412.8 ± 494.9	507.3 ± 813.4	0.807

* Cockcroft-Gault Equation (Cockcroft et al., 1976).

Abbreviations: BMI=Body Mass Index; STS-PROM Score=Society of Thoracic Surgeons Predicted Risk of Mortality; EuroSCORE II =European System for Cardiac Operative Risk Evaluation II; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Hemoglobin; CPB=*Cardiopulmonary Bypass;* ICU=*Intensive Care Unit;* APACHE II=*Acute Physiology and Chronic Health Evaluation II;* SOFA=*Sequential Organ Failure Assessment.*

The initial laboratory values of both groups are shown in **Table 3**. Between the two groups, patients with mesenteric ischemia tended to have higher D-dimer levels (1.5 ± 0.8 mg/L vs. 0.8 ± 0.9 mg/L; p = 0.130) and lower platelet counts (248.0 ± 60.7 per µL vs. 459.8 ± 912.9 per µL; p = 0.615) compared to the control group, although these differences were not statistically significant.

Table 3. Baseline laboratory characteristics of target population.

Variable, n (%) or mean ±SD	Me-Is (n=5)	Non Me-Is (n=20)	p Value
Prothrombin Time (Quick), sec	93.0 ± 19.9	97.3 ± 17.4	0.639
Partial Thromboplastin Time (PTT), sec	29.8 ± 3.3	30.45 ± 3.7	0.726
International Normalized Ratio (INR)	1.1 ± 0.1	1.0 ± 0.2	0.826
Fibrinogen, g/L	4.3 ± 1.5	3.8 ± 1.0	0.375
D-Dimer, mg/L	1.5 ± 0.8	0.8 ± 0.9	0.130
Calcium, mmol/L	2.2 ± 0.2	2.3 ± 0.1	0.162
Platelet Count, pro µL	248.0 ± 60.7	459.8 ± 912.9	0.615
Antithrombin III (ATIII), %	102.5 ± 10.6	105.4 ± 9.7	0.604

Figure **11** shows the time course of the concentrations of intestinal fatty acid-binding protein (I-FABP) and interleukin-6 (IL-6) between the group with mesenteric ischemia (Me-Is) and the control group (non-Me-Is). In patients with mesenteric ischemia, there was a significant increase in I-FABP concentration at the time of admission to the intensive care unit (ICU) compared to the control group (2252.25 ± 1582.69 pg/ml vs. 17116.20 ± 18185.41 pg/ml, 95%CI [-22847.99 to -6879.90], p = 0.006). This difference remained significant even 12 hours after ICU admission (1030.79 ± 1099.92 pg/ml vs 16998.15 ± 20346.39 pg/ml, 95%CI [-24804.38 to -7130.34], p = 0.030).

For interleukin-6 (IL-6), there was initially no significant difference between the two groups at ICU admission (1100.14 ± 1207.94 pg/ml vs 2933.50 ± 3019.41 pg/ml, 95%CI [-5544.49 to 1877.77]; p = 0.249). However, 12 hours after ICU admission, the IL-6 concentration was significantly higher in the Me-Is group than in the control group (533.57 ± 1107.23 pg/ml vs 2585.86 ± 2801.84 pg/ml, 95%CI [-5498.10 to 1393.52], p= 0.179) (**Figure 11**). The data thus indicate more pronounced intestinal damage and inflammatory response in patients with mesenteric ischemia.

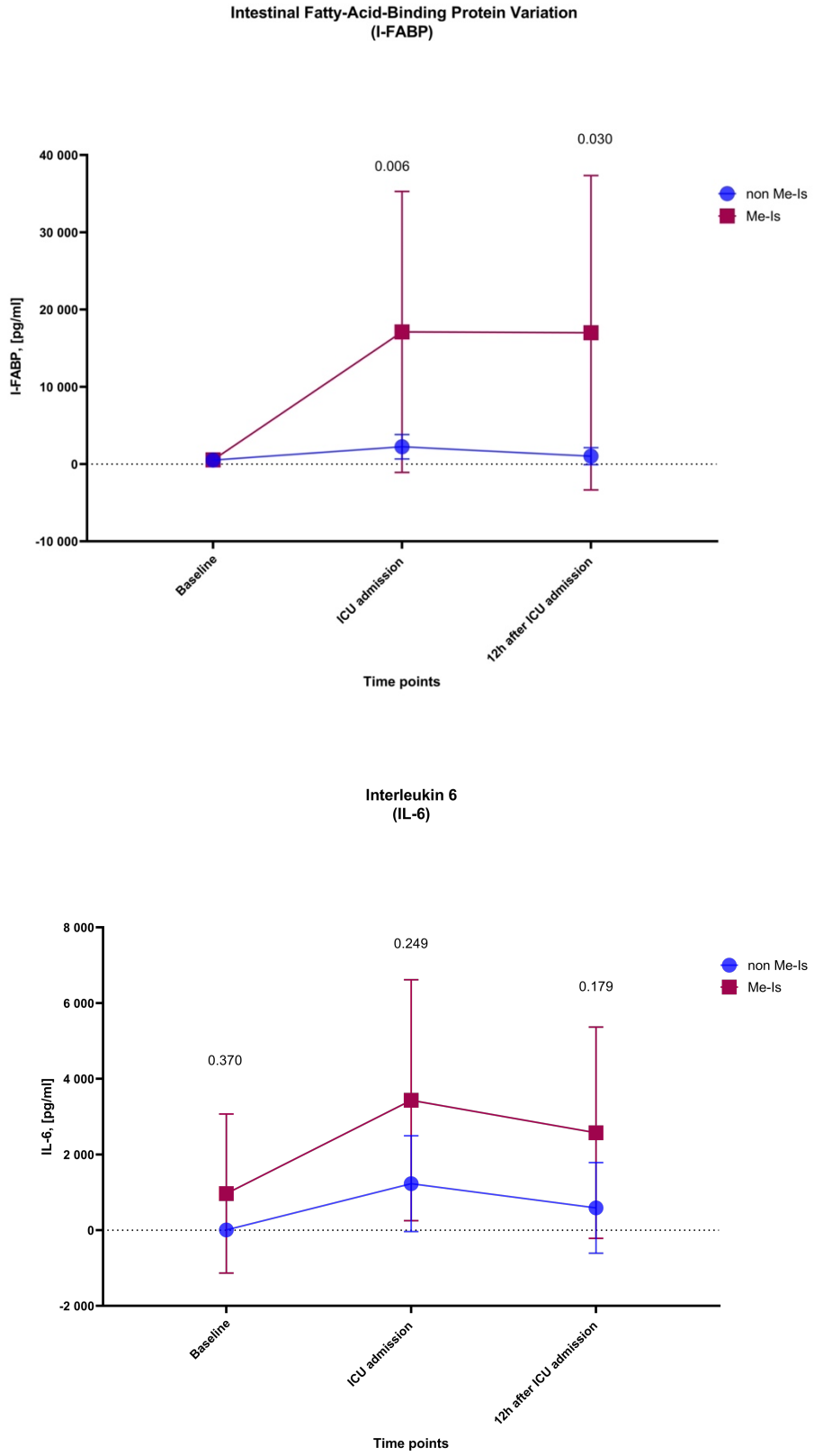

Figure 11. Time course of serum concentrations of the intestinal fatty acid-binding protein (I-FABP, left) and interleukin-6 (IL-6, right) in the group with mesenteric ischemia (Me-Is) compared to the control group (Non Me-Is).

Figure 12 shows the progression of the enzymatic coagulation activation markers thrombin-antithrombin complex (TAT), prothrombin fragments 1+2 (F1+2), and D-dimers.

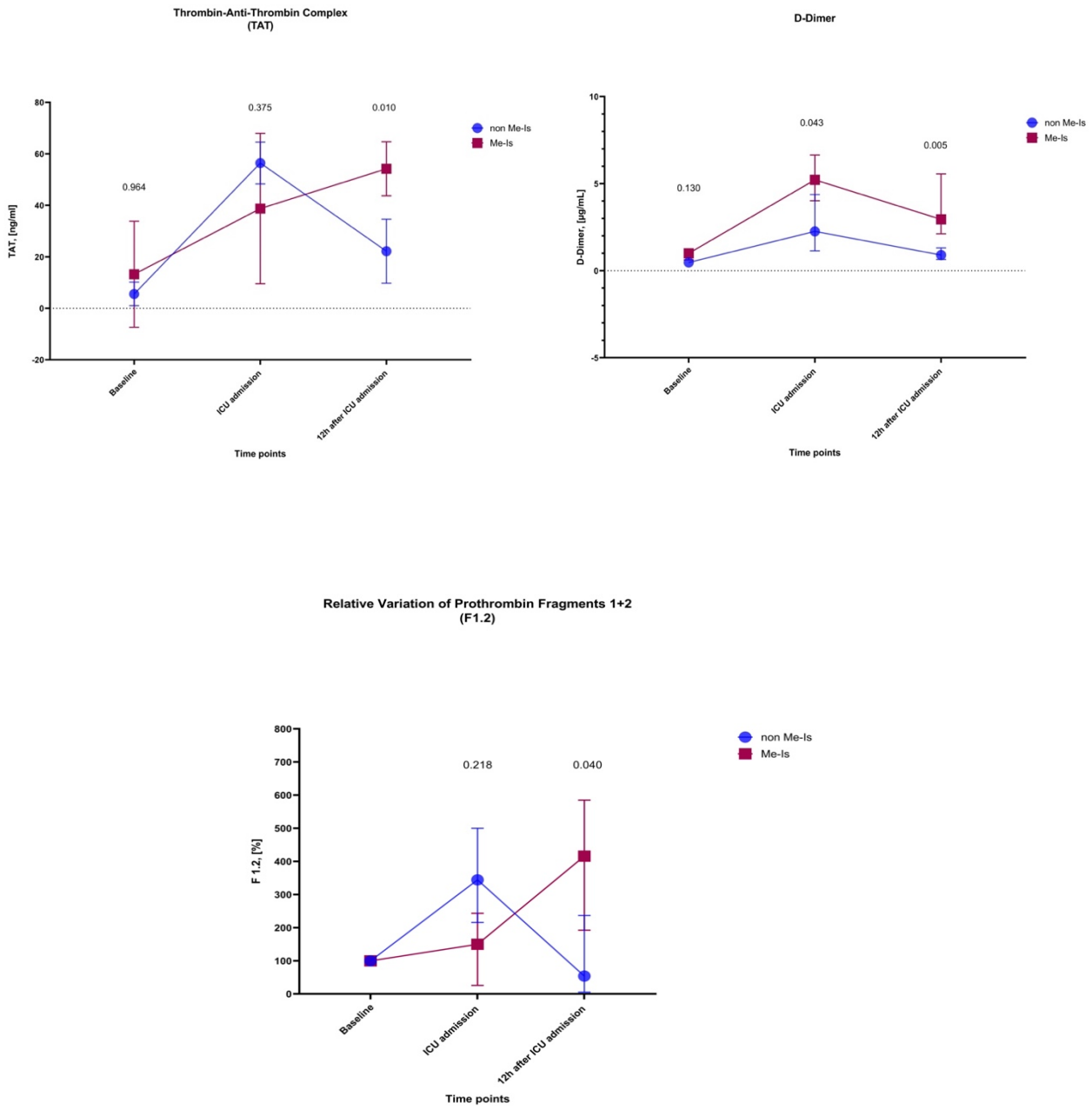

Figure 12. Time course of the enzymatic coagulation activation markers thrombin-antithrombin complex (TAT, a), prothrombin fragments 1+2 (F1+2, b) and D-dimers (c).

There were no significant differences in the levels of thrombin-antithrombin complex (TAT) between the groups at the time of ICU admission (p = 0.375). However, 12 hours after ICU admission, the TAT value was significantly higher in the Me-Is group than in the control group (54.20 ±10.49 vs 22.18±12.43 ng/ml, 95%CI [7.46 to 38.50], p = 0.010).

In contrast, the absolute values of prothrombin fragments 1+2 (F1+2) on admission to the ICU were significantly higher in the control group than in the Me-Is group (1.19±0.04 vs 0.49 ± 0.47 ng/ml, 95%CI [-0.57 to 1.44], p=0.047). However, the relative changes in F1+2 concentrations within 12 hours of ICU admission showed a 3.9-fold increase from baseline in the Me-Is group (394.2 ± 231.6%) compared to only a 1.1-fold increase in the control group (114.7 ± 144.9%). This difference was statistically significant (95%CI [-448.45 to -110.54], p = 0.040).

The concentrations of D-dimers were already significantly higher in the Me-Is group at the time of admission to the ICU (5.3±1.3 vs 3.0±2.1 µg/ml, 95%CI [-4.46 to -0.25], p = 0.043). This difference was even more pronounced 12 hours after ICU admission (3.7±1.8 vs 1.2±0.8 µg/ml, 95%CI [-3.66 to -1.34], p = 0.005). In addition, there was also a significantly increased D-dimer level in the Me-Is group compared to the control group (**Figure 13**). Taken together, these results suggest that patients with mesenteric ischemia have more pronounced activation of clotting.

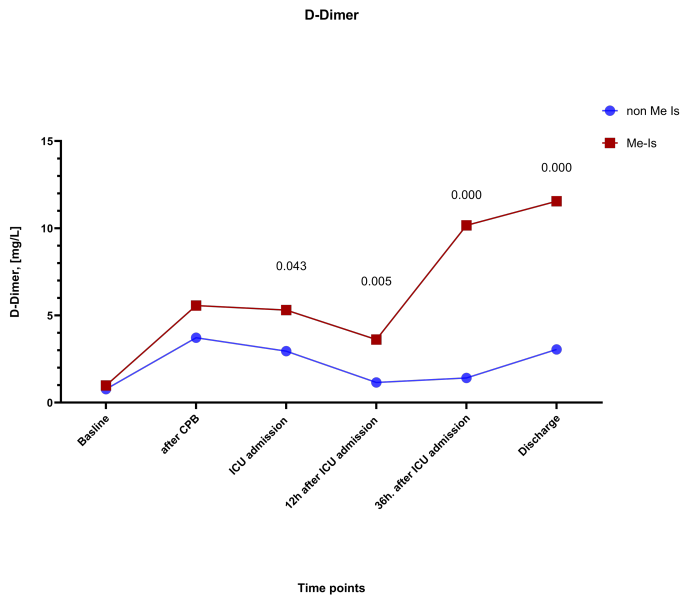

Figure 13. Time course of D-dimers.

4.2.2 Global test for prediction of bleeding

The parameters of thrombin generation ("velocity index", "time to peak", "lag time", "endogenous thrombin potential (ETP)" and "peak thrombin") showed no significant differences over time between patients with mesenteric ischemia (Me-Is) and the control group (non-Me-Is) (**Figure 14**). Thus, there was no association between the occurrence of mesenteric ischemia and altered thrombin-generating parameters.

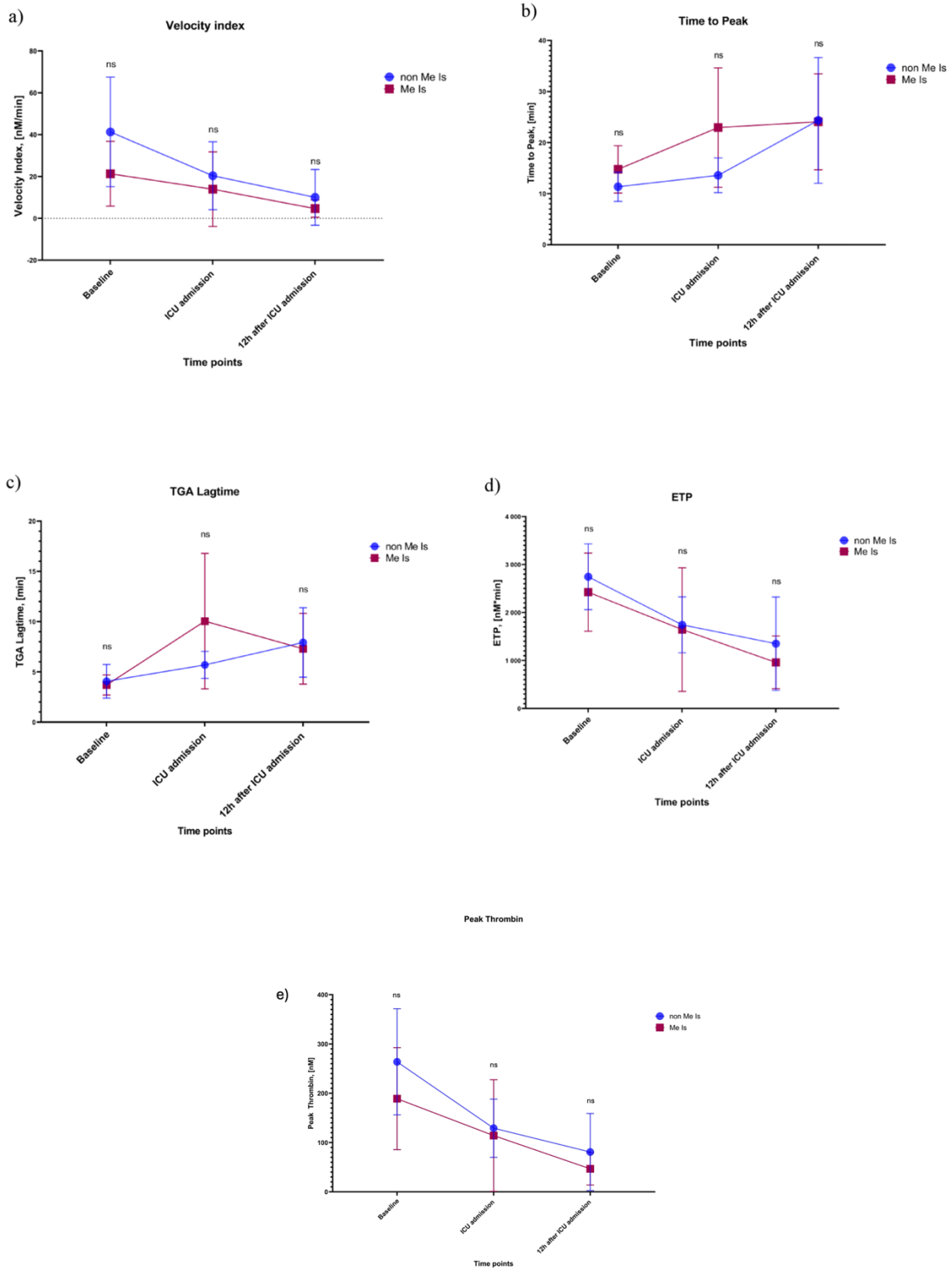

Figure 14. shows the results of the thrombin genesis test (TGA) over time. a) Velocity index; b) Time to peak; c) TGA lag time; d) ETP- endogenous thrombin potential; e) Peak Thrombin.

The courses of the coagulation markers fibrinogen, partial thromboplastin time (PTT), antithrombin III (ATIII), and platelet count are shown in **Figures 15 and 16**. While there were no significant differences between the two patient groups for fibrinogen, which is an indicator of coagulation activation and acute phase reactions, PTT, a parameter of the intrinsic coagulation cascade, was significantly prolonged in the Me-Is group from 36 hours after admission to the ICU. ATIII, which reflects physiological anticoagulation and hepatic synthesis performance, was significantly reduced in the Me-Is group as early as 12 hours after ICU admission. Overall, these results suggest increased coagulation activation, consumption coagulopathy, and relevant ATIII utilization occur later in patients with mesenteric ischemia. The platelet count remained unchanged throughout the entire course in both groups.

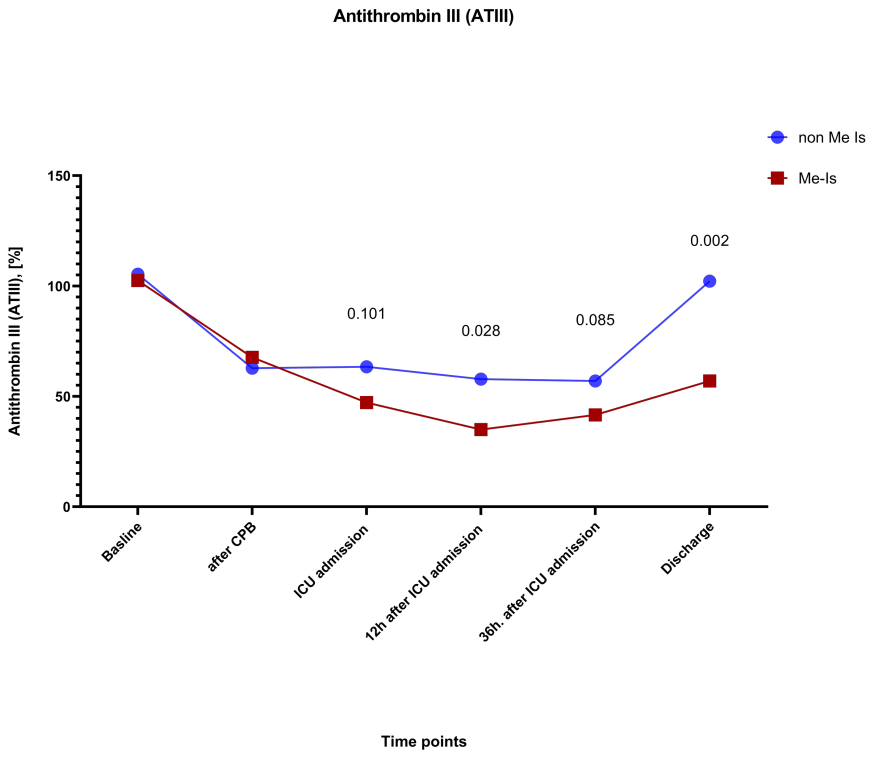

Figure 15. Time course of antithrombin III (ATIII).

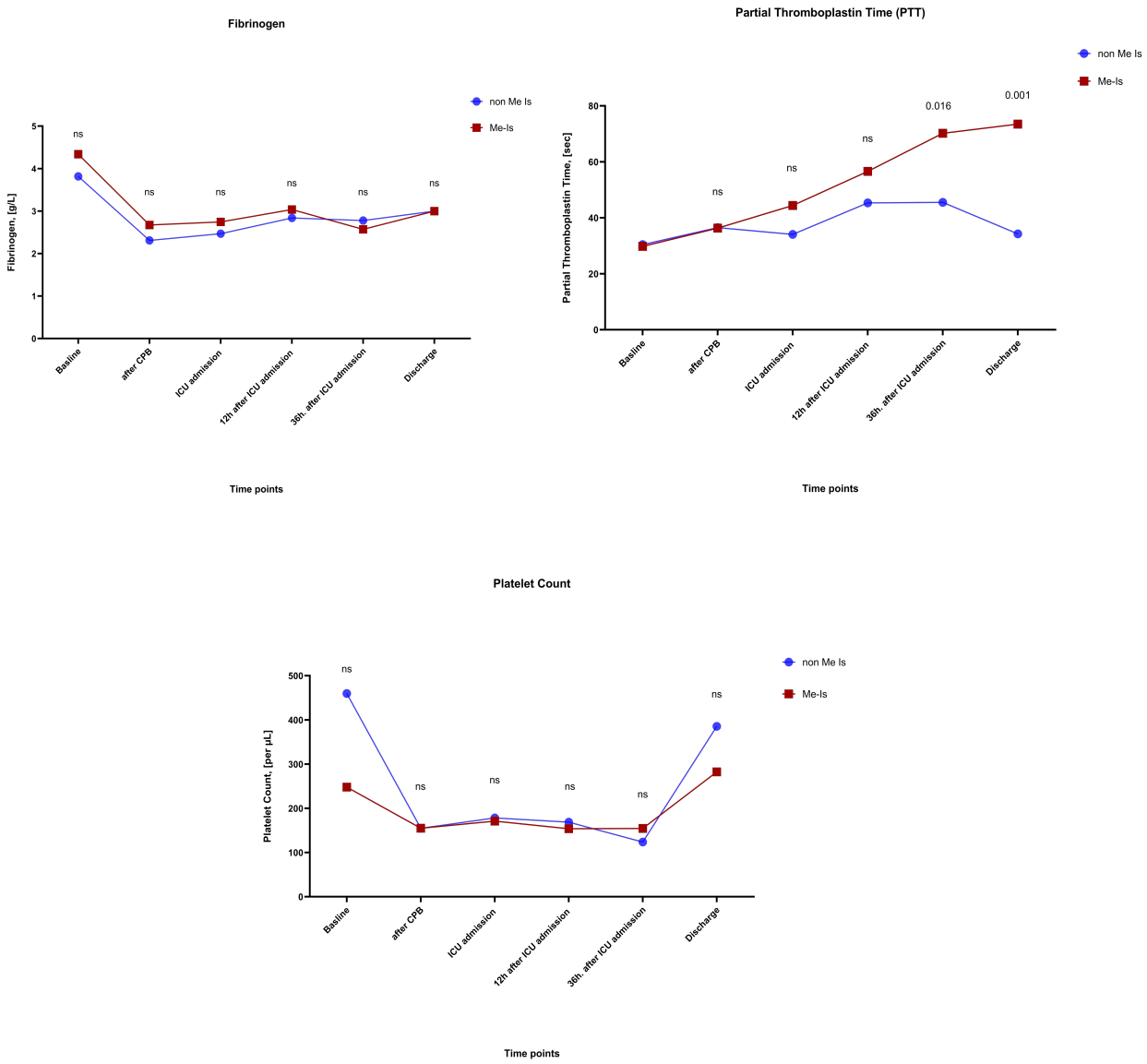

Figure 16. Time courses of fibrinogen, partial thromboplastin time (PTT), and platelet count.

5. Discussion

5.1 I-FABP as a predictive biomarker for intestinal ischemia after cardiac surgery

The intestinal fatty acid-binding protein (I-FABP) is an innovative and previously underrepresented biomarker in cardiovascular intensive care. Originally described as an indicator of intestinal hypoxia in gastrointestinal diseases, I-FABP is increasingly being recognized as important in the context of extracorporeal circulation and systemic hypoperfusion. Acute mesenteric ischemia (AMI) after cardiac surgery remains a clinically challenging diagnosis with high mortality; early detection via sensitive biomarkers could open a therapeutic window.

Our research group was able to convincingly show that I-FABP levels were significantly above the threshold of 1.421 pg/mL in all patients with confirmed AMI. In contrast, the two control groups – patients with abdominal symptoms without ischemia ("disease controls") and patients without any intestinal symptoms – showed no significant increases. The diagnostic performance of I-FABP was clearly superior to conventional parameters (e.g., lactate, leukocytes), which was reflected in a sensitivity of 100%.

These clinical results confirm previous data from Kanda et al. (2001) obtained from a rat model that demonstrated a rapid increase in I-FABP after reversible occlusion of the superior mesenteric artery. In our cohort, a similar course was observed in a patient with NOMI in which the I-FABP concentration decreased rapidly after prostavasin-assisted improvement of perfusion. This observation supports the hypothesis that I-FABP can be used not only for diagnosis, but also as a parameter for monitoring intestinal perfusion.

In the future, I-FABP could be used in a multimodal diagnostic pathway with imaging techniques, clinical scores, and coagulation parameters to identify patients at an early stage with a high risk of mesenteric hypoxia. The ease of measurability in serum and the short half-life make the marker particularly attractive for intensive care medicine. A serial determination during the course of treatment could also help to objectively monitor the effectiveness of therapeutic interventions.

5.2 Hypercoagulability as a pathophysiological correlate of mesenteric ischemia

The pathophysiological basis of AMI extends far beyond mechanical vascular occlusion. Endothelial dysfunction, which is induced by inflammatory mediators (e.g., IL-6, TNF-α) and triggers thrombin generation via the expression of tissue factor, is central to the mechanism (Paulus et al., 2011). This promotes a local prothrombotic change in the micromilieu that manifests clinically in microthrombi and subclinical disseminated intravascular coagulation.

Our laboratory analytical data showed a consistent pattern of early hypercoagulability in AMI patients. **Figure 17** illustrates the significant increase in prothrombin fragments F1+2, a sensitive surrogate marker for the activation of prothrombinase. The magnitude of the increase was significant in ischemic patients compared to non-ischemic subjects (p=0.040).

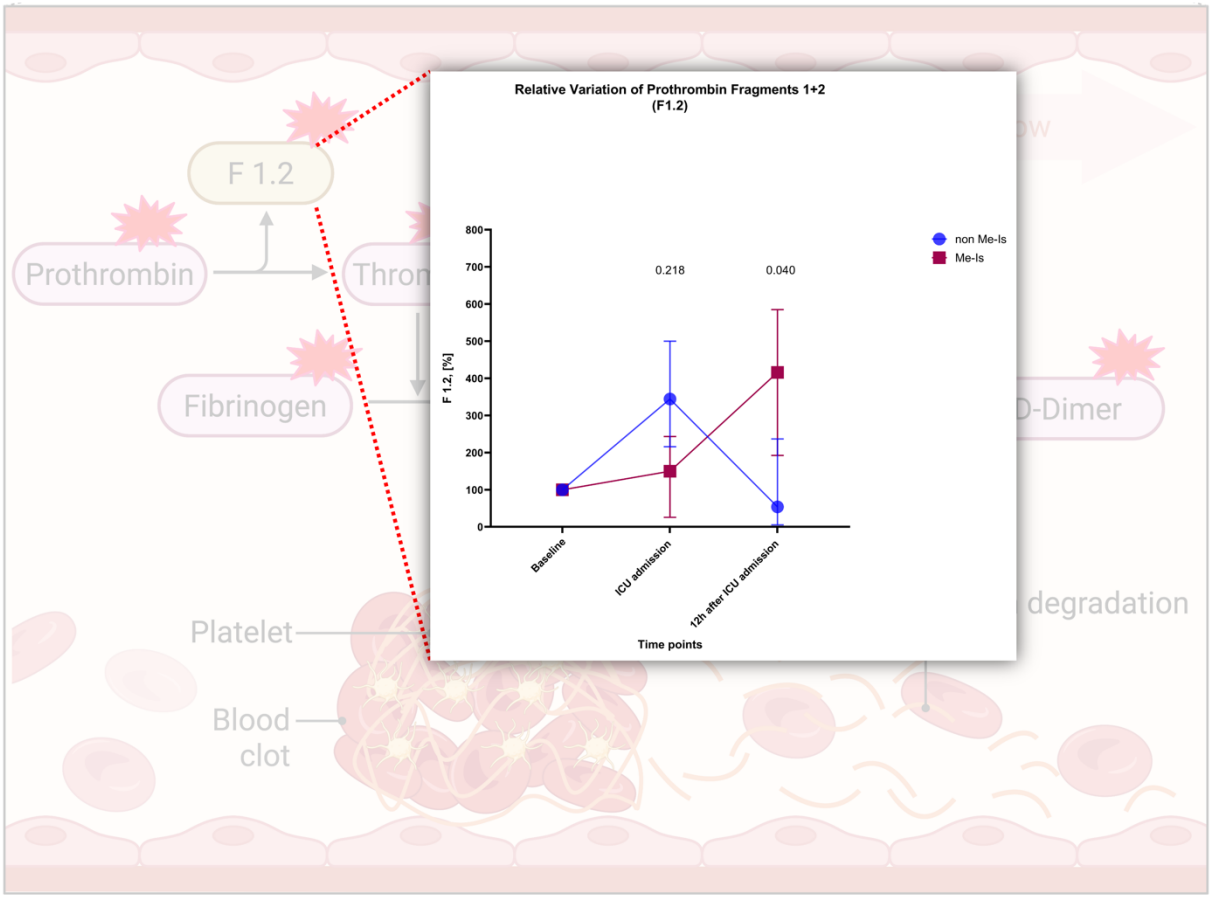

Figure 17. Significant increase in prothrombin fragments F1+2.

Thrombin-antithrombin complexes (TAT) also increased significantly (**Figure 18 lower panel,** p=0.010), which underpins active thrombin formation. These molecules form during acute thrombin release and bind to antithrombin III, whose concentration tended to decrease in the

ischemic group (**Figure 18 upper panel**, p=0.028), which also suggests that consumption coagulopathy develops.

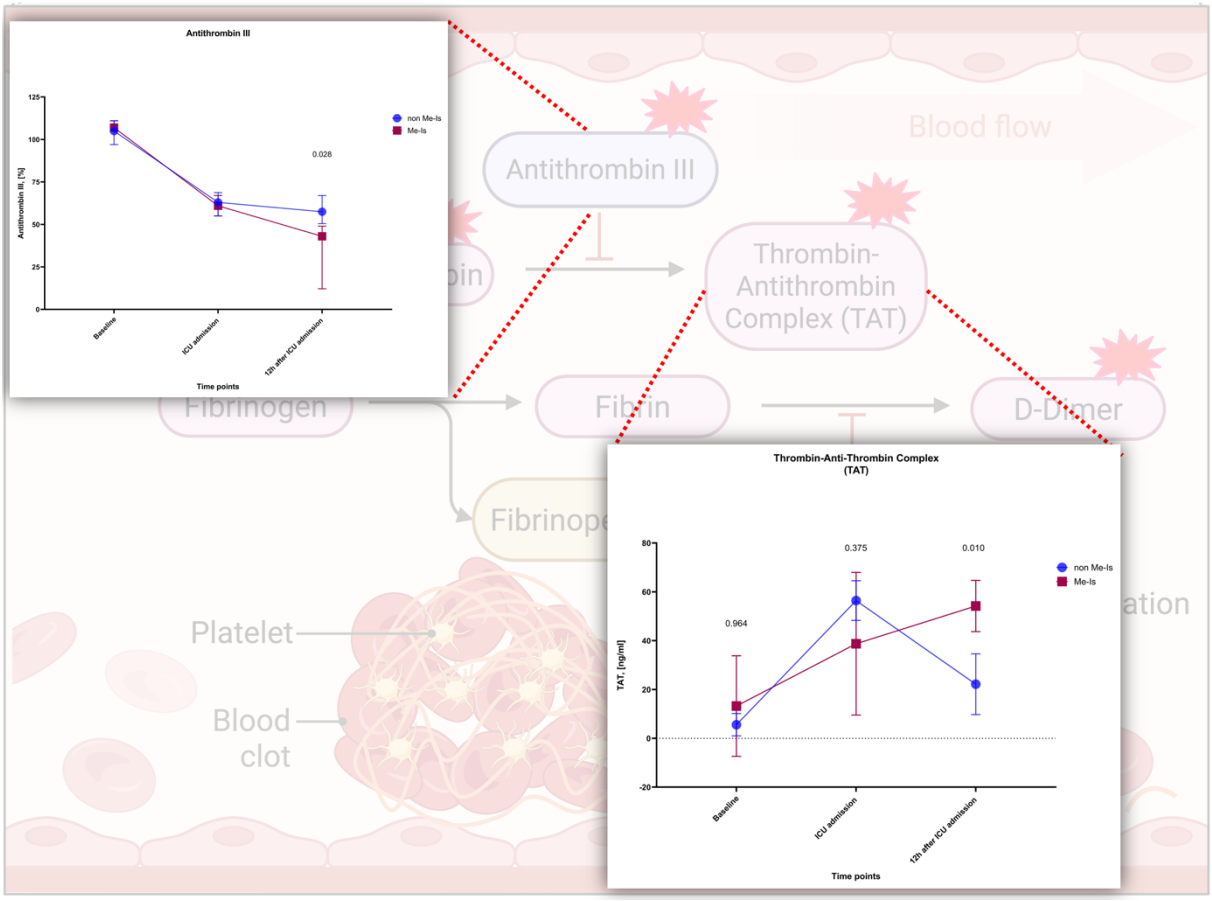

Figure 18. Significant change in TAT and ATIII levels 12 hours after ICU admission.

D-dimer levels showed a clear increase in ischemic patients (p=0.043 to 0.005), indicating a simultaneous fibrinolytic response (**Figure 19, right panel**). Interestingly, fibrinogen levels remained within the normal range (**Figure 19 left panel**), making manifest DIC unlikely at this time.

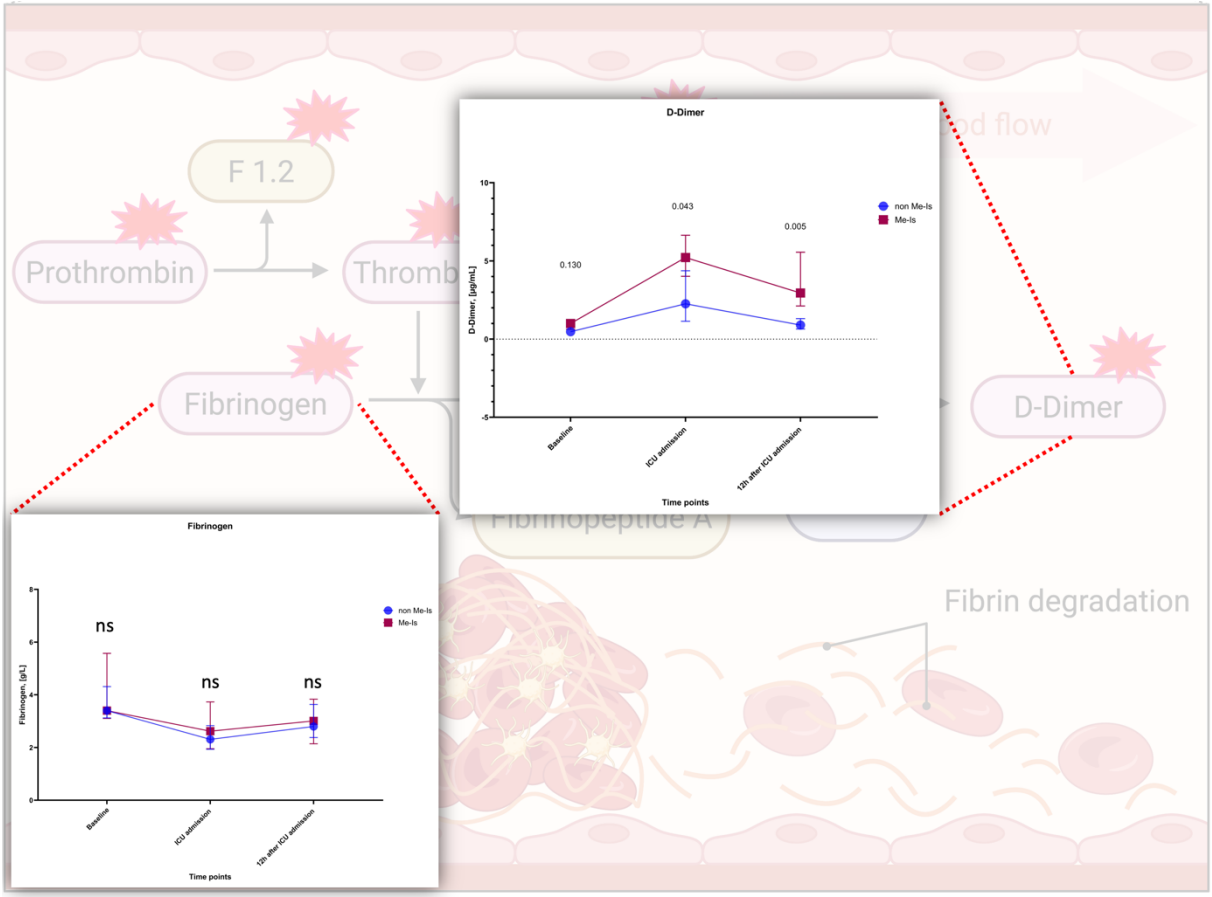

Figure 19. Activated coagulation as well as fibrinolysis, with no significant difference in fibrinogen formation.

This constellation suggests an early stage of subclinical hypercoagulopathy, which is characterized by increased thrombin formation and fibrinolysis, but without consumptive coagulopathy. The pathophysiological picture of this phase is visually summarized in **Figure 20** and represents the transition from vascular inflammation to coagulopathy to thrombotic events.

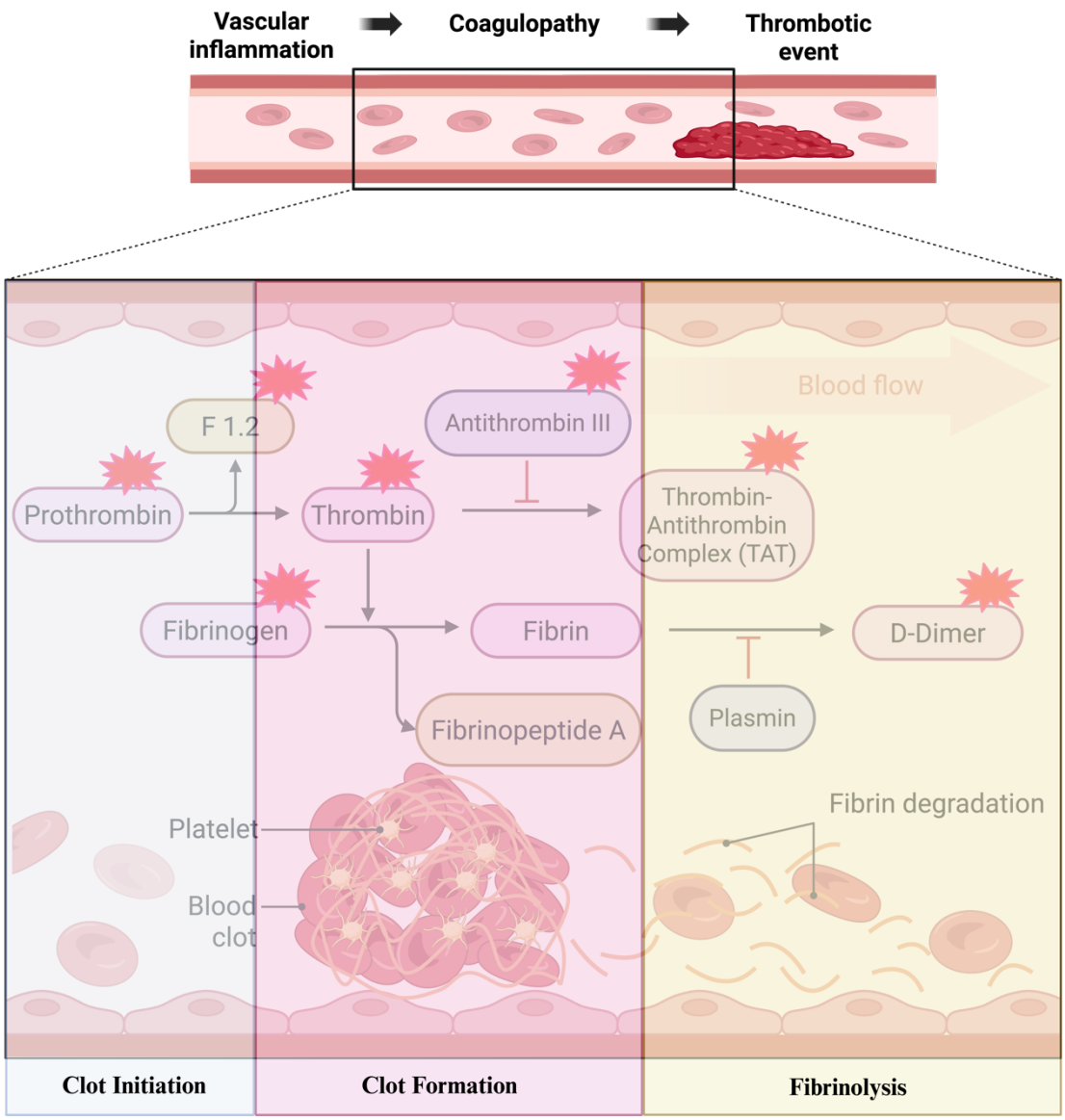

Figure 20. Pathophysiological vicious circle in acute mesenteric ischemia.

Legend: Ischemia-induced hypoxia leads to the release of inflammatory mediators such as interleukin-6 (IL-6), which activate the coagulation cascade. The resulting hypercoagulability promotes the formation of microthrombi in the intestine. These microthrombi enhance local hypoperfusion, which perpetuates oxygen deficiency. A self-reinforcing pathobiological circuit develops, which exacerbates intestinal ischemia and increases the risk of transmural necrosis.

5.3 Clinical relevance

The early phase of hypercoagulability opens up a therapeutic window of opportunity that – if detected in time – can be used to prevent progression to manifest DIC and transmural intestinal necrosis. Our data suggest that early therapeutic anticoagulation with unfractionated heparin, possibly also combined with antithrombin-enhancing agents, could lead to a significant improvement in intestinal perfusion. The standard administration of low-molecular heparin (NMH) does not seem to be sufficient in this context, as NMH has a primarily preventive effect but may not have an adequate therapeutic effect in acute thrombin overproduction (Nemeth, 2019). A future approach could be a risk-adapted anticoagulation strategy, in which patients are given intensified anticoagulation based on their TAT and F1+2 levels. Such marker-based strategies would enable more "personalized" coagulation management.

At the same time, attention must be paid to the balance between antithrombotic efficacy and the risk of bleeding, especially in the postoperative setting. This requires interdisciplinary algorithms that include anesthesia, surgery, and intensive care. However, clinical studies to determine the optimal time and dosage for therapeutic anticoagulation are still lacking and should be initiated urgently.

5.4 Conclusion

The present results show that I-FABP is a highly sensitive biomarker for the early detection of mesenteric ischemia, especially in patients after cardiac surgery. Simultaneous detection of coagulation activity via F1+2, TAT, D-dimer, and antithrombin III provides a dynamic assessment of prothrombotic activation and identifies those patients who may benefit from early anticoagulation.

This work lays the foundation for an integrated diagnostic and therapeutic protocol that combines biomarkers, clinical observation, and targeted anticoagulation. The implementation of such a protocol could contribute to reducing mortality from AMI after cardiac surgery in the medium term.

Further investigations should examine the extent to which point-of-care-based coagulation diagnostics (e.g., ROTEM, thromboelastic profiles) correlate with systemic markers such as I-

FABP and TAT and allow bedside-controlled intervention. The goal must be not only to identify critical ischemic events retrospectively, but also to prevent them prospectively.

5.3 Study limitations

This study has some limitations, as it is based on a non-randomized analysis of prospectively collected registry data from a comparatively small group of patients, all of whom were treated at a single center. Despite the use of propensity score matching, there were still significant differences in preoperative characteristics between the two treatment groups.

6. Summary

Background: Cardiac surgery is considered to be a hypercoagulable state with an increased incidence of thromboembolic events. In acute mesenteric ischemia (Me-Is), plasma coagulation markers may have additional diagnostic relevance perioperatively.

Methods: Out of 500 consecutive cardiac surgery patients, 25 patients with hyperinflammatory (IL-6 >600 ng/l) and metabolic acidosis (lactate >4 mmol/l) were retrospectively matched 1:4 into Me-Is (n=5) and control (n=20) groups. Blood samples collected before surgery, upon ICU admission and 12 hours after ICU admission were assessed for hemostatic parameters, including fibrinogen, D-dimer, thrombin-anti-thrombin complex (TAT), prothrombin fragments 1+2 (F1+2). All samples were also evaluated in thrombin generation assays, and intestinal fatty-acid-binding protein (I-FABP) was assessed as a marker for Me-Is.

Results: Baseline levels of hemostatic markers in the two groups were similar. TAT levels were significantly increased in the Me-IS group at 12h after ICU admission, respectively (54.20 ±10.49 vs 22.18±12.43 ng/ml, p=0.010). In contrast, at ICU admission, absolute F1+2 values were significantly increased in the control group (1.19±0.04 vs. 0.49 ± 0.47 ng/ml, p=0.047). However, the relative F1+2 values of the Me-Is group (394.2±231.6%) vs. the control group (114.7±144.9%) within 12 hours after ICU admission were 3.9- vs. 1.1-fold higher than baseline (p=0.040). Postoperatively, significantly higher levels of I-FABP and of D-dimers were observed in the Me-Is group vs. controls at ICU admission, (17116.2±18185.4 vs. 2252.3±1582.7 pg/ml [p=0.006] and 5.3±1.3 vs. 3.0±2.1 µg/ml [p=0.043], respectively) and 12 hours after ICU admission (16998.2±20346.3 vs. 1030.8±1100.0 pg/ml [p=0.030] and 3.7±1.8 vs. 1.2±0.8 µg/ml [p=0.005], respectively). No significant differences were observed for thrombin generation (TGA, peak value, ETP) between the two groups.

Conclusion: Our findings suggest that TAT and F1+2 levels are promising candidate markers for evaluating coagulability after cardiac surgery. High levels of activation markers suggest a temporary stage of hypercoagulability immediately after surgery in Me-Is patients.

7. Zusammenfassung

Hintergrund: Herzchirurgische Eingriffe induzieren einen hyperkoagulablen Zustand mit erhöhter Inzidenz thromboembolischer Ereignisse. Bei akuter mesenterialer Ischämie (Me-Is) könnten plasmatische Gerinnungsmarker zusätzliche diagnostische Relevanz in der perioperativen Phase besitzen.

Methodik: Aus 500 konsekutiven herzchirurgischen Patient:innen wurden retrospektiv 25 Personen mit hyperinflammatorischem Profil (IL-6 >600 ng/l) und metabolischer Azidose (Laktat >4 mmol/l) identifiziert. Diese Kohorte wurde im Verhältnis 1:4 einer Me-Is-Gruppe (n=5) und einer Kontrollgruppe (n=20) zugeordnet. Präoperativ, bei Aufnahme auf die Intensivstation (ICU) sowie 12 Stunden postoperativ wurden hämostaseologische Parameter analysiert: funktionelles Fibrinogen, D-Dimer, Thrombin-Antithrombin-Komplex (TAT), Prothrombinfragmente 1+2 (F1.2). Zusätzlich erfolgten Thrombin-Generations-Assays (TGA) sowie die Bestimmung des intestinalen Fettsäure-bindenden Proteins (I-FABP) als Me-Is-Marker.

Ergebnisse: Die Ausgangswerte der Gerinnungsparameter zeigten keine Gruppenunterschiede. 12 Stunden nach ICU-Aufnahme lagen die TAT-Spiegel in der Me-Is-Gruppe signifikant höher (54,20 ±10,49 vs. 22,18±12,43 ng/ml; p=0,010). Bei ICU-Aufnahme wies die Kontrollgruppe hingegen erhöhte absolute F1.2-Werte auf (1,19±0,04 vs. 0,49±0,47 ng/ml; p=0,047). Relativ betrachtet stiegen die F1.2-Werte in der Me-Is-Gruppe innerhalb von 12 Stunden jedoch um das 3,9-Fache (394,2±231,6%) gegenüber dem Ausgangswert, während die Kontrollgruppe nur einen 1,1-fachen Anstieg (114,7±144,9%) zeigte (p=0,046). Postoperativ fielen in der Me-Is-Gruppe sowohl I-FABP als auch D-Dimere signifikant höher aus: Bei ICU-Aufnahme 17116,2±18185,4 vs. 2252,3±1582,7 pg/ml (p=0,006) und 5,3±1,3 vs. 3,0±2,1 µg/ml (p=0,043); nach 12 Stunden 16998,2±20346,3 vs. 1030,8±1100,0 pg/ml (p=0,030) und 3,7±1,8 vs. 1,2±0,8 µg/ml (p=0,005). Thrombin-Generations-Assays (Peak, ETP) ergaben keine Gruppenunterschiede.

Schlussfolgerung: TAT und F1.2 zeigen sich als vielversprechende Parameter zur Evaluation der Gerinnungsaktivierung nach Herzoperationen. Die ausgeprägte Dynamik dieser Marker deutet bei Me-Is-Patient:innen auf eine transiente Hyperkoagulabilitätsphase unmittelbar postoperativ hin. Eine frühzeitige Identifikation könnte die Risikostratifizierung für mesenteriale Ischämien optimieren.

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9. Supplement

Glossary of abbreviations

Abbreviation	Definition
AMI	Acute Mesenteric Ischemia
APACHE II	Acute Physiology and Chronic Health Evaluation II
ATIII	Antithrombin III
AUC	Area Under the Curve
BMI	Body Mass Index
CPB	Cardiopulmonary Bypass
CT	Contrast-Enhanced Computed Tomography
CTA	Computed Tomography Angiography
DIC	Disseminated Intravascular Coagulation
ECC	Extracorporeal Circulation
eGFR	Estimated Glomerular Filtration Rate
ETP	Endogenous Thrombin Potential
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II
F1+2	Prothrombin Fragments 1+2
HbA1c	Glycated Hemoglobin
IABP	Intra-Aortic Balloon Pump
ICU	Intensive Care Unit
I-FABP	Intestinal Fatty Acid-Binding Protein
IL-6	Interleukin-6
LVEF	Left Ventricular Ejection Fraction
Me-Is	Mesenteric Ischemia
NMH	Low-Molecular Heparin
NOMI	Non-Occlusive Mesenteric Ischemia
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
PPP	Platelet-Poor Plasma
PTT	Partial Thromboplastin Time
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
STS-PROM Score	Society of Thoracic Surgeons Predicted Risk of Mortality
TAT	Thrombin-Antithrombin Complexes
TGA	Thrombin Generation Analysis
TF	Tissue Factor
TFPI	Tissue Factor Pathway Inhibitor
TNF-α	Tumor Necrosis Factor Alpha
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Diagnosis
VTE	Venous Thromboembolism

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Materials and Equipment

Materials and Equipment	Manufacturer
Hycult®Biotech high-sensitivity ELISA kit (HK406)	Hycult Biotechnology B.V., Uden, The Netherlands
Citrate-containing blood collection tubes	Sarstedt AG & Co. KG, Nümbrecht, Germany
Polypropylene storage tubes	Eppendorf AG, Hamburg, Germany
Enzygnost™ F1+2 (monoclonal) ELISA kit	Siemens Healthineers, Marburg, Germany
Enzygnost™ TAT micro ELISA kit	Siemens Healthineers, Marburg, Germany
RC Low reagents	Technoclone GmbH, Vienna, Austria
Ceveron® s100 coagulation analyzer	Technoclone GmbH, Vienna, Austria
SPSS® Statistics version 27.0	IBM® Corporation, Armonk, NY, USA
GraphPad Prism version 10.0.0	GraphPad Software, San Diego, CA, USA
REDCap electronic data capture tools	Vanderbilt University, Nashville, TN, USA

Affirmation

Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten sowie ethische, datenschutzrechtliche und tierschutzrechtliche Grundsätze befolgt. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Die vorgelegte Arbeit wurde weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf welches direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt und indirekt an der Entstehung der vorliegenden Arbeit beteiligt waren. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.

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Ort, Datum Unterschrift

Declaration of Honour

I hereby declare that I have completed the present work independently and without unauthorised assistance or use of other than stated aids. All text passages quoted or paraphrased from published or unpublished writings, and all information based on oral statements, have been identified as such. In the research I conducted and mentioned in the dissertation, I have adhered to the principles of good scientific practice as laid down in the 'Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis', and have complied with ethical, data protection, and animal welfare principles. I assure that no third party has received direct or indirect monetary benefits for work related to the content of the submitted dissertation. The submitted thesis has not been presented in the same or a similar form to any other examination authority be it domestically or abroad, for the purpose of a doctorate or any other examination procedure. All material taken from other sources and persons, which was used or directly referenced in the dissertation, has been identified as such. In particular, all individuals who were directly or indirectly involved in the composition of the present work have been named. I agree to have my dissertation verified by a plagiarism detection software or an internet-based software program.

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Curriculum vitae

Publication list

First and Senior authorship

Book Contribution

Taghiyev ZT (Senior contributor), Arneth B, Altrawy A, Mohamed R , Ghazy A, Hamdy D, Abdel-Ghany S., Sabit H. Organoid Culture System as Innovative Model of Heart Stem Cell-Based Cardiac Development and Diseases in The Cardiovascular System (Under Review, ID: CCM-M-10779809, The Cardiovascular System, 2025, ISBN: 9780443298905 - Elsevier Verlag)

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Congress contributions

2025 DGTHG

- Combined Treatment for Coronary Artery Disease and Aortic Valve Stenosis.
- Is Negative Pressure Wound Therapy better for sternal wound healing?
- Relationship between Hypercoagulability and Mesenteric Ischemia early after Cardiac Surgery.

2024 EACTS, DGK, DCK, Chirurgische Forschungstage, DGTHG

- Intestinal Damage Marker as a Potential Predictor of Early Mortality after Cardiac Surgery.
- Impact of the SGLT2 inhibitor on patients undergoing cardiac surgery.
- A Cost-Benefit Analysis of Endoscopic versus Conventional Vein Harvesting in Cardiac Surgery Based on the German DRG System.
- Intestinal Damage Marker as a Potential Predictor of Early Mortality after Cardiac Surgery
- Experimental evaluation of Esmolol-crystalloid cardioplegia compared to blood cardioplegia with Calafiore in rat hearts.

2023 DGTHG

- Permanent Pacemaker Implantation after Combined Percutaneous Treatment for Coronary Artery Disease and Aortic Valve Stenosis (TAVR PCI vs. SAVR CABG) .
- Prognostic value of the renal function in patients treated with transcatheter aortic valve replacement and percutaneous coronary intervention versus surgical aortic valve replacement with coronary artery bypass grafting (TAVR PCI vs. SAVR CABG).

2021 DGTHG

- Long-Term Results of Left Atrial Appendage Amputation in Ptients Undergoing Concomitant AF Ablation during Cardiac Surgery.

2018 DGTHG

- Early-Term Results of Rapid-Deployment Aortic Valve Replacement versus Standard Bioprosthesis Implantation Combined with Coronary Artery Bypass Grafting.

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Sir Isaac Newton

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