Clinical benefits and prognostic value of heart-type fatty acid binding protein, myocardial creatine kinase and specific right ventricular echocardiographic parameters for risk stratification of normo ...

Forkmann, Mathias

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

MATHIAS FORKMANN

CLINICAL BENEFITS AND PROGNOSTIC VALUE OF HEART-TYPE FATTY ACID BINDING PROTEIN, MYOCARDIAL CREATINE KINASE AND SPECIFIC RIGHT VENTRICULAR ECHOCARDIOGRAPHIC PARAMETERS FOR RISK STRATIFICATION OF NORMOTENSIVE PATIENTS WITH PULMONARY EMBOLISM

DOCTORAL DISSERTATION

Split, Croatia 2021.

Institution: Department of Cardiology, Klinikum Coburg, Ketschendorfer Str. 33, 96450 Coburg, Germany
Mentor: Prof. Markus Ketteler

ACKNOWLEGDEMENTS

The completion of this work would not have been possible without support and help of many people. First of all, I would like to thank my mentor *Prof. Ketteler*, his invaluable assistance contributed greatly to my work. The head of the department of cardiology, *Prof. Brachmann*, taught me to look always forward and impressed me with his visions of the future. I greatly appreciate the excellent support from *Assoc. Prof. Ivana Kolcic* from Croatia on the PhD journey. I will forever be thankful to *Prof. Wunderlich* who supported me in my first years in cardiology and electrophysiology in Dresden. Special "Thank you" goes for *Martin Langer* with his patience in explaining me statistics. I am also glad to have the support of many good friends, *Maik Behnke, Steffen Hahn, Gregor Thoß,* and *Marko Swoboda*, one of the smartest people I know.

Zuguterletzt möchte ich mich bei meiner Familie bedanken, meinen *Eltern*, die mich unablässig unterstützt haben, meinen Bruder *Sebastian*, für seine unermüdliche Unterstützung an dieser Arbeit.

Und schließlich ganz besonders Dir, meiner liebsten *Dorothea*, die sich geduldig um unsere Kinder *Moritz, Carla* und *Kolja* gekümmert hat, während ich noch bis spät in die Nacht am Arbeiten war.

Dein M.

Contents

List of Abbrevations

A‘	maximum late-diastolic myocardial velocity
AUC	area under curve
BMI	body mass index
BP	blood pressure
CK	creatine kinase
CK-MB	creatine kinase isoenzyme muscle-brain type
DVT	deep vein thrombosis
E‘	maximum early-diastolic myocardial velocity
EF	ejection fraction
ELISA	enzyme linked immunosorbent assay
ESC	european society of cardiology
GFR	glomerular filtration rate
FN	false negative
FP	false positive
HR	heart rate
H-FABP	heart-type fatty acid binding protein
ICOPER	international cooperative pulmonary embolism register
IQR	interquartile range
LA	left atrium
LV	left ventricle
MDCT	multi-detector computed tomographic
mmHg	millimeters of mercury
MRI	magent resonance tomography
mTDI	myocardial tissue doppler imaging
NPV	negative predictive value
NS	non significant
(NT-pro) BNP	(N-terminal pro-) brain natriuretic peptide
OR	odds ratio
pCO_2	partial pressure of carbon dioxide
PE	pulmonary embolism
PESI	pulmonary embolism severity index
PFO	patent foramen ovale
pO_2	partial pressure of oxygen

PPV	positive predictive value
PSM	paradoxical septal movement
RA	right atrium
ROC	reciever operating characteristic
RV	right ventricle
RVD	right ventricular dysfunction
RVSP	right ventricular systolic pressure
SaO_2	oxygen saturation
S‘	maximum systolic myocardial velocity
sPESI	simplified pulmonary embolism severity index
TAPSE	tricuspid annular plane systolic excursion
TnT/I	troponin T/I
VTE	venous thrombembolism

List of Figures

List of Tables

1 Introduction

1.1 Pulmonary Embolism

1.1.1 From Past To Present

In 1856 the Berlin physician and pathologist Rudolf Virchow formulated the still valid fundamental aetiology and pathogenesis of deep vein thrombosis (DVT) and thus also of the pulmonary embolism (PE) (1) . Today, these are well known under the term of Virchow's triad and include:

- Stasis: stagnancy or change in flow of blood
- Hypercoagulability: changes in blood composition and coagulation factors
- Intima lesion: injuries of the inner layer of the vessel wall

All known causes of DVT can be attributed to these three elemental changes. Because of the similarities in aetiology and pathogenesis PE and DVT are summarized as venous thromboembolism (VTE).

PE is a relatively common disease, with an incidence ranging from 60 to 112 per 100,000 inhabitants of the United States (2), and is the third most common cause of death among patients with cardiovascular diseases (3). In six European states with a total population of 454.4 million, almost 300 000 cases of PE and more than 370 000 VTE related deaths were estimated in 2004 on the basis of an epidemiological model (4). Patients are at particular risk in the acute stage of the disease, with 30-day mortality rates in excess of 15% for PE associated with shock and/or hypotension (5). PE is difficult to diagnose because of the wide range of presentations of the disease. Among those patients who die of PE, 94% do so before diagnosis (6). Thus, acute PE may still be an under-diagnosed disease, especially when largely stable circulatory conditions prevail. The unspecific symptomatology may lead to delayed claiming medical aid and could be a reason for the relatively high mortality in these patients. In contrast, the progress of non-fulminanten PE is extremely heterogeneous compared to the fulminant form. The spectrum ranges from absolutely uncomplicated to unexpectedly lethal, which complicates the decision regarding the further therapy form (7).

Therefore, in recent years, clinical research has increasingly focused on the non-fulminant PE. A central issue includes the identification of haemodynamically stable patients, who need a more intensive monitoring and therapy because of risk of complications. The risk stratification uses different approaches by combining clinical prediction models with various cardiac laboratory meters (biomarkers) and imaging techniques.

Among the biomarkers are mainly the cardiac troponins T and I (TnT / I) and the natriuretic peptides (BNP or the cleavage product NT-proBNP), which have been and are being investigated with regard to their prognostic relevance for PE. While these biomarkers in other diseases of the heart (e.g., myocardial infarction and heart failure) are now part of the diagnostic standard and also could be used for therapy control, they are still unsatisfactory in identifying high-risk patients in the acute phase of non-fulminant PE.

A new approach to risk stratification has been the discovery of the heart-specific fatty acid binding protein (H-FABP). It is a new biomarker that is already being used successfully in early cardiac infarction diagnostics because of its favorable kinetics and organ specificity (8) and, unlike other biomarkers, indicates a poor prognosis in all forms of acute coronary syndrome (9). In contrast, recently the use of H-FABP to estimate the prognosis in PE has become the focus of clinical research. H-FABP seems to be superior to all other markers in the first 30 days after the acute event (10, 11). Even though available for a long time and being part of the lab routine in patients presenting with chest pain, Creatine Kinase Isoenzyme MB (CK-MB) has not been studied in detail for risk assessment in PE. Stein and colleagues were the first to investigate the potential prognostic value of CK-MB, cTnT, and right ventricular dilatation in normotensive patients with PE. Although their findings were statistically not significant, CK-MB tended to be a stronger predictor of death than cTnT, and the combination of CK-MB, cTnT and echocardiography seemed particularly indicative (12).

Using echocardiography, it is possible to assess ventricular size relationships and dynamic parameters of right heart function objectively. For this purpose, newer methods such as the measurement of systolic excursion of the tricuspid valve plane (Tricuspid Annular Plane Systolic Excursion, TAPSE) or myocardial tissue Doppler Imaging (mTDI) are suitable.

While conventional Doppler echocardiography visualizes and measures blood flow velocities, mTDI measures ventricular tissue contraction velocities to provide functionally assessable contraction and relaxation behavior of the ventricles. Although mTDI for the left ventricle (LV) is already an established procedure, the assessment of the right ventricle (RV) with TDI has hardly been done so far. This fact underlines the long-underestimated hemodynamic importance of RV function (13).

1.1.2 Epidemiology

Deep vein thrombosis and pulmonary embolism represent the two forms of VTE and they are often considered together from an epidemiological point of view. Venous thromboembolism is the third most frequent cardiovascular disease after acute myocardial infarction and stroke (14)

with an overall annual incidence of 100–200 per 100 000 inhabitants (4, 15). In acute phase VTE may be lethal or can lead to chronic disease and disability (16, 17), but it is also often preventable. The most serious clinical presentation of VTE is acute PE. Pulmonary embolism is a major cause of mortality, morbidity, and hospitalization in Europe with an annual incidence rate from 39-115 per 100 000 population (18). For DVT the incidence rates range from 53-162 per 100 000 population (19). However, incidence rates for PE are difficult to determine due to overlaps between VTE, PE and DVT (5). Furthermore, the epidemiology of PE is difficult to specify because it may remain asymptomatic, or its diagnosis may be an incidental finding (4). In some cases, sudden death is the first presentation of PE (20). Cohen et al. designed an epidemiological model for six European states, which estimate 317,000 VTE-related deaths per year in 2004 (4). Only 7% of the patients who died early were correctly diagnosed with PE before death. The risk of PE increased in patients older than 40 years compared with younger patients and the risk approximately doubles with each subsequent decade (21). Taken together, the epidemiological data on VTE, and in particular the PE, shows that the frequency, importance and seriousness of these diseases may be significantly underestimated.

1.1.3 Pathophysiology

The pathophysiology of PE is a complex, highly dynamic event in which the clinical, radiological and laboratory findings can change very rapidly. The principal process of PE is almost always the influx of a thromboembolus into the pulmonary circulation via the RV (Figure 1.1).

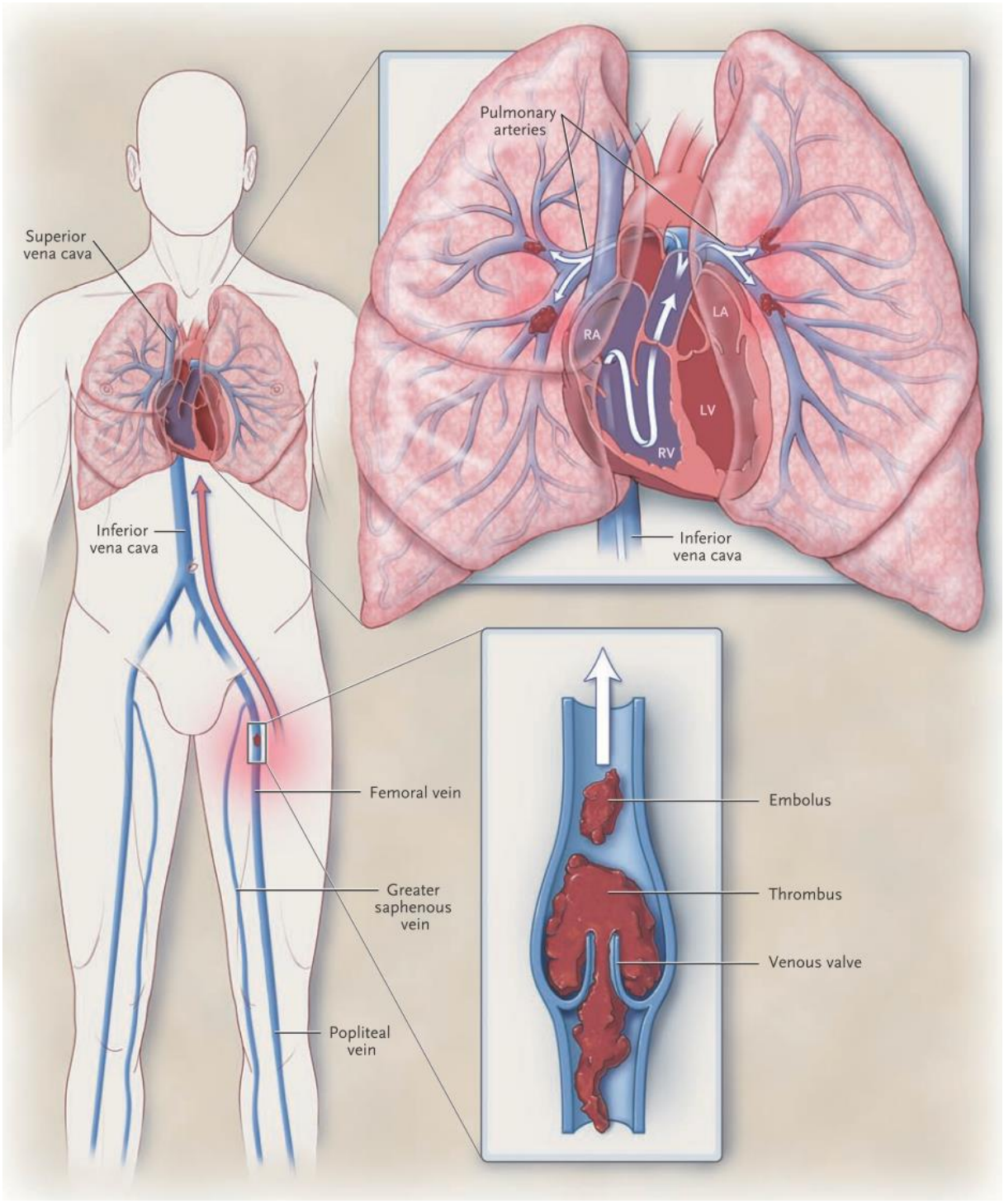

Figure 1. 1 Pathophysiology of Pulmonary Embolism (22)

The embolus is most likely from the deep leg veins. With higher place of origin or higher spread of the embolus the risk for a PE increases (22). The obstruction of the pulmonary vessels results in severe disturbances of the hemodynamics and gas exchange, the extent of which depends on the size of the embolus, the number of affected pulmonary vessels, the pre- and concomitant diseases and the available compensatory (neurohumoral) adaptation mechanisms of the patient

(23). Only if more than 30–50% of the total cross-sectional area of the pulmonary arterial bed is occluded by thromboemboli, the pulmonary artery pressure increases (24).

Disorders of hemodynamics (Figure 1.2) results from the abrupt increase of vascular resistance in the pulmonary circulation. This increase is due to mechanical obstruction and hypoxic vasoconstriction and triggered by constrictive acting substances like thromboxane A2 and serotonin (25). This results in an increase in the afterload. The RV, which normally only needs to generate pressures up to a maximum of 20 mmHg for pulmonary circulation, suddenly has to overcome pressures in excess of 40 mmHg (-80 mmHg). Under extreme conditions, the RV pressure can rise above that of the LV. In case of patent foramen ovale, a right-left shunt increased the risk of paradoxical embolism with subsequent stroke.

The abrupt increased afterload initiates a pathological process leading to right ventricular dilation, which alters the contractile properties of the RV myocardium via the Frank-Starling mechanism, tricuspid regurgitation, and ultimately to right heart failure. Despite signs of the RVD the systemic blood pressure can initially kept constant and suggest a stable hemodynamic status by neurohumoral compensation mechanisms and sympathetic activation conditions, and then suddenly turn into a therapy-resistant hypotension with circulatory failure (23).

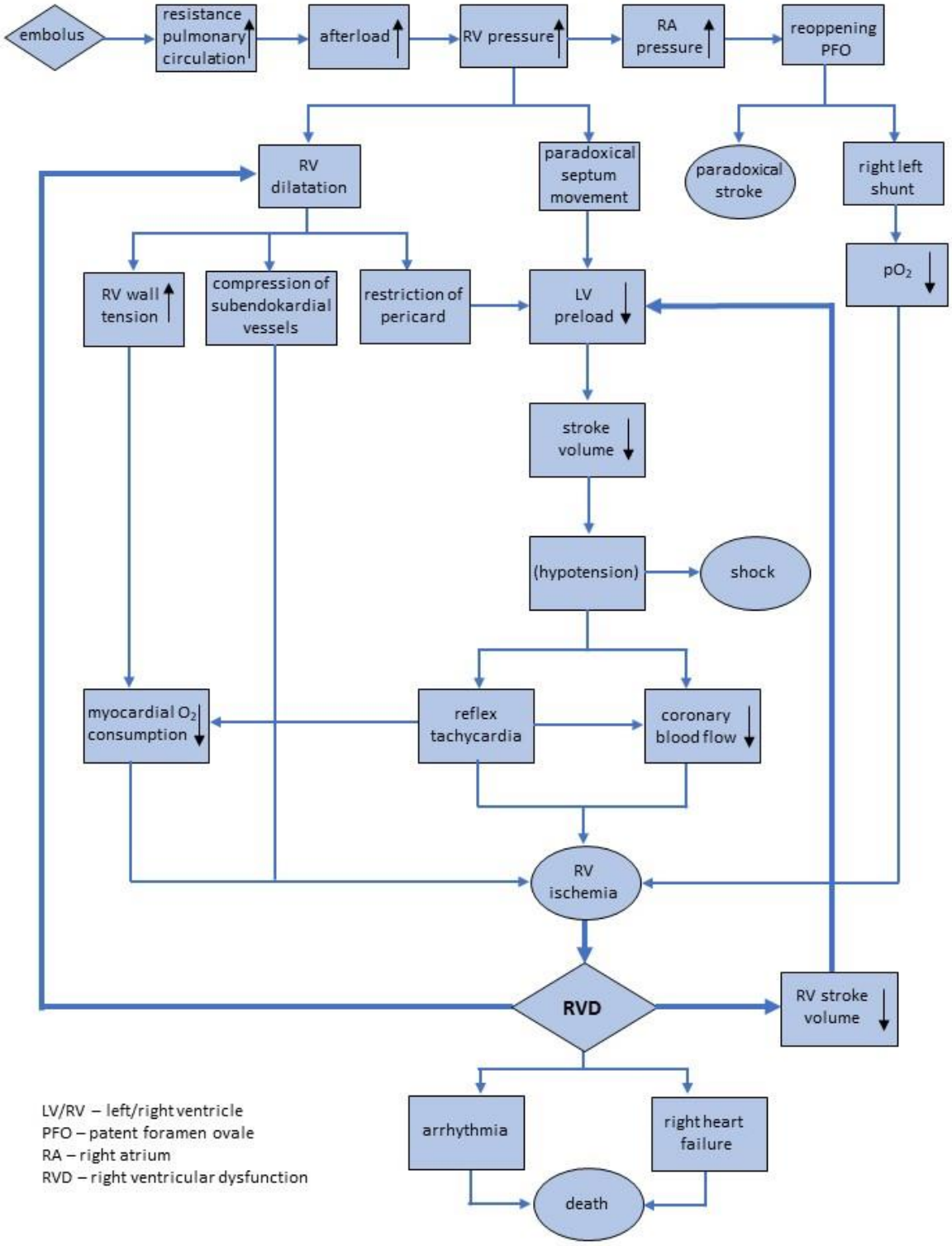

Figure 1. 2 Hemodynamic impact of PE, modified (22, 23, 26)

Because RV and LV function complement each other and are interdependent (interventricular dependency), a disorder of one ventricle also affects the function of the other. Thus, the RV dilation due to the increase in afterload is the basis for all other hemodynamic effects. Caused by an extension of the systole of the RV, the RV is still contracting while the LV is already starting to relax. The pressure in the RV at this time is higher than that at the beginning of the diastole LV. This results in a shift of the interventricular septum in the direction to LV (paradoxical septal movement) and obstructs the filling of LV, followed by reduced preload and decreased LV stroke volume. Furthermore, right-left shunt on atrial level arise and so the oxygen partial pressure in the blood (pO2) continues to reduce. In order to keep the cardiac output constant, a reflex-tachycardia occurs. At same time RV dilation leads to an increase in wall tension with increased oxygen consumption and compression of subendocardial vessels and the right coronary artery. A circulus vitiosus emerges because the increase in oxygen consumption while reducing myocardial perfusion (reduced stroke volume of LV, tachycardia shortens diastole) and pO2 (shunt) leads to subendocardial ischemia and RV microinfarction, which further restricts the ejection fraction (27). Microinfarction are the cause of the increase in myocardial necrosis markers such as TnT / I and H-FABP (28), while dilatation of RV leads to the release of BNP and NT-proBNP (29, 30).

A predominant consequence of haemodynamic disturbance in PE is respiratory failure (31). Low cardiac output leads to desaturation of the mixed venous blood. Additionally, zones of reduced flow in obstructed vessels, combined with zones of overflow in the capillary bed served by non-obstructed vessels, result in ventilation–perfusion mismatch, which contributes to hypoxaemia. A right-to-left shunting through a PFO can be detected by echocardiography in about one-third of patients. This is caused by an inverted pressure gradient between the right atrium and left atrium and may lead to severe hypoxaemia and an increased risk of paradoxical embolization and stroke (32).

Proinflammatory mediators and other vasoactive substances contribute to pathophysiology, but their importance is controversial (5). The local release of histamine and serotonin results in broncho- and vasoconstriction, and changes in vascular permeability (pleural effusion, edema) and surfactant function. Pulmonary shunts can arise directly from the local release of mediators such as the platelet-activating factor (33). A number of other cytokines like tumor necrosis factor (TNF-α) and interleukins (IL-1β) mediate activation of adhesion molecules (CAMs) and the migration of leukocytes into the interstitium (34). These in turn maintain and reinforce the above changes and can promote the development of pneumonia after pulmonary infarction in extensive PE (33).

1.1.4 Risk Factors

Although VTE is idiopathic in up to 25% of the cases (35), numerous risk factors (Table 1.1, (26)) directly or indirectly favor the development of VTE (secondary VTE).

Table 1. 1 Risk factors for VTE (26)

Strong association risk factors (odds ratio >10)	**Moderate association risk factors (odds ratio 2–9)**	**Weak association risk factors (odds ratio <2)**
Fracture of lower limb	Arthroscopic knee surgery	Bed rest >3 days
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)	Auto–immune diseases	Diabetes mellitus
Hip or knee replacement	Blood transfusion	Hypertension
Major trauma	Central venous lines	Increasing age
Myocardial infarction (within previous 3 months)	Chemotherapy	Immobility due to sitting (e.g. prolonged car or air travel)
Previous venous thromboembolism	Congestive heart or respiratory failure	Laparoscopic surgery (e.g. cholecystectomy)
Spinal cord injury	Erythropoiesis-stimulating agents	Obesity
	Hormone replacement therapy (depends on formulation)	Pregnancy
	In vitro fertilization	Varicose veins
	Cancer (highest risk in metastatic disease)	
	Oral contraceptive therapy	
	Paralytic stroke	
	Postpartum period	
	Thrombophilia	

In particular, the interaction of several risk factors is problematic because the overall risk increases exponentially. Insights into the pathophysiological meaning complement and confirm the original concept of the Virchow's triad. Accordingly, in principle, acquired risk factors can be different from hereditary risk factors. The current concept assumes that VTE almost always results from an interaction between patient (such as age) and situational (such as surgery) factors (26). Worthy of mention is the fact that more than 50% of all VTE cases were preceded by hospitalization. All other risk factors together account for about 25% of all VTE, the rest is idiopathic.

1.1.5 Clinical Presentation

The clinical signs of nonfulminant PE are non-specific (Table 1.2, adapted from Pollack et al. (36)), as many diseases similarly manifest.

Table 1. 2 Clinical characteristics of patients with suspected PE (36)

Feature	**PE confirmed (n= 1880)**	**PE not confirmed (n=528)**
Dyspnoea, %	50	51
Pleuritic chest pain, %	39	28
Cough, %	23	23
Substernal chest pain, %	15	17
Fever, %	10	10
Haemoptysis, %	8	4
Syncope, %	6	6
Unilateral leg pain, %	6	5
Signs of DVT, %	24	18

In most of the patients, PE is suspected on the basis of chest pain, dyspnoea, pre-syncope or syncope, and/or haemoptysis (36, 37). Arterial hypotension and shock are rare but important clinical presentations. Syncope is infrequent, however it may occur regardless of the presence of haemodynamic instability (38). Finally, PE can be completely asymptomatic and be discovered incidentally during diagnostic work-up for another disease or at autopsy.

1.1.6 Classification

The PE is classified into three risk groups according to the guidelines of the European Society of Cardiology (ESC) fom 2019 for prediction of early (in-hospital or 30-day) mortality (26). For the risk assessment additional to clinical, imaging and laboratory findings a clinical score

is recommended, the Pulmonary Embolism Severity Index (PESI). This complexed score required 11 differently weighed parameters for risk assessment. There is also a more practicable and simplified version (sPESI) available. The strength of the sPESI (Table 1.3, modified (26)) lies in the reliable identification of patients at low risk for 30 day mortality (26).

Table 1. 3 Simplified pulmonary embolism severity index (sPESI) (26)

Parameter	Simplified version
Age	1 point (if age > 80 years)
Cancer	1 point
Chronic heart failure	1 point
Chronic pulmonary disease	1 point
Pulse rate ≥ 110 bpm	1 point
Systolic BP < 100 mmHg	1 point
Arterial oxyhaemoglobin saturation < 90%	1 point
Risk	
	0 points = 30 day mortality risk 1.0% (95% CI 0.0 – 2.1%)
	≥ 1point(s) = 30 day mortality risk 10.9% (95% CI 8.5 – 13.2%)

The classification of pulmonary embolism severity and level of clinical risk is show in Table 1.4. (modified (26)). The study was initiated and conducted prior to the introduction of PESI in the guidelines. However, the current guidelines recommend that patients with signs of RVD or elevated cardiac biomarkers, despite low low PESI or an sPESI of 0, should be classified into the intermediate-risk group (26). The reason is that the early all cause mortality rates (1.8% for RVD and 3.8 for elevated troponin levels (39)) were in the lower range of those previously reported for PE patients with intermediate-risk (40).

Table 1. 4 Classification of mortality of patients with acute PE. Modified according to Konstantinides and colleagues (26)

Early mortality risk		**Risk parameters**			
		Hemodynamic instability	Clinical parameters of PE severity and/or comorbidity: sPESI ≥ 1	Signs of RV dysfunction in echocardiography or MDCT	Elevated cardiac troponin levels
High		+	(+)	+	(+)
Intermediate	Intermediate-high	-	+	Both positive	
	Intermediate-low	-	+	Either one (or none) positive	
Low		-	+	Both negative	

High-risk pulmonary embolism is characterized by overt hemodynamic instability and warrants immediate advanced therapy, including consideration of fibrinolysis (26). Hemodynamic instability is defined as cardiac arrest, obstructive shock (systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥ 90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP < 90 mmHg or a systolic BP drop ≥ 40 mmHg for > 15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis). Early mortality in this group is at least 25% in patients with hypotension, more than 50% in shock and over 65% in patients requiring resuscitation (41, 42). In contrast, for patients presenting without systemic hypotension or hemodynamic compromise, standard anticoagulation is generally considered adequate treatment (43). However, patients who have acute right ventricular dysfunction and myocardial injury without overt hemodynamic compromise may be at intermediate risk for an adverse early outcome (26). Mortality in these patients varied in the literatur between 5% and 16% (5, 44). These patients (referred to hence-forth as patients with intermediate-risk pulmonary embolism) may also be candidates for early reperfusion therapy (45). The low-risk group includes patients with stable circulatory conditions and without signs of right ventricular dysfunction (RVD) or myocardial damage, and standard anticoagulation is generally considered adequate treatment (43). The mortality risk is below 1% (5).

1.1.7 Diagnostic and Therapy

For the assessment of clinical probability of PE, clinical likelihood scores for (Wells or revised Geneva score) are very well established (46, 47). The Wells score has been validated extensively using both a three-category scheme (low, moderate, or high clinical probability of PE) and a two-category scheme (PE likely or unlikely). The revised Geneva score is also simple and standardized.

In addition to the vital parameters, simple diagnostic tests include chest x-ray, ECG and arterial blood gas analysis. Although typical variations for PE exist, these parameters are all unspecific. For example, the S_1Q_3 (T_3) type in ECG, which is often regarded as pathognomonic, only occurs in 12% of the cases (48).

Diagnostic Imaging

At present, mainly the following imaging methods are used:

- Lower limb compression venous ultrasonography
- Multi-detector computed tomographic (MDCT) angiography
- Ventilation–perfusion scintigraphy
- Echocardiography

MDCT replaces invasive and risky conventional pulmonary angiography as the method of choice (26). Simultaneously, in the context of risk stratification, this method allows the evaluation of prognostically relevant parameters, such as the extent of RV dilation (49).

Ventilation–perfusion scintigraphy is a well-studied and validated method of examination. It is recommended in guidelines in cases of contraindication to MDCT and should be preferred over MDCT to avoid unnecessary radiation, in particular in younger and female patients in whom thoracic CT may raise the lifetime risk of breast cancer (26).

In patients with fulminant PE, bedside echocardiography is the diagnostic method of choice, as doing CT and waiting for laboratory results (D-Dimere) would take too long. Furthermore, hemodynamically relevant differential diagnoses (e.g., severe LV dysfunction, acute valvular dysfunction, aortic dissection, or pericardial tamponade) may also be excluded. Of importance is echocardiography for risk stratification of patients with nonfulminant PE, when for example RVD or free-floating thrombi are diagnosed in the RV (26).

Biomarkers

D-dimers are determined routinely in suspected PE. The cleavage products from endogenous fibrinolysis virtually exclude the presence of an PE in a negative test result due to a high

negative predictive value (50). Conversely, the D-dimer test is not suitable for diagnosing PE / DVT, since elevated plasma levels are also found in elderly, hospitalized and tumor patients, for example after trauma, surgical intervention, pregnancy and renal insufficiency (26). The new ESC guidelines recommend a D-dimer test, using an age-adjusted cut-off or adapted to clinical probability as an alternative to the fixed cut-off levels and they recommend no measurement of D-dimers in patients with a high clinical probability, as normal result does not exclude PE (26).

The determination of TnT / I, BNP / NT-proBNP and more recently H-FABP is important for risk stratification (see 1.2 Risk stratification).

Therapy

A rapid, risk-adapted initiation of therapy is essential for survival, as most patients die in the first hours after the initial event due to prompt recurrent embolism (51, 52). In case of clinical suspicion, anticoagulation should already be initiated in order to reduce the mortality and recurrence rate (53). The acute-phase treatment consists of administering parenteral anticoagulation [unfractionated heparin, low molecular weight heparin, or fondaparinux] over the first 5–10 days. When oral anticoagulation is started in a patient who is eligible for a NOAC (apixaban, dabigatran, edoxaban or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist (26). The initiation of a vitamin K antagonist should overlap with parenteral heparin.

In unstable high-risk patients, rapid restoration of pulmonary perfusion in the form of systemic thrombolysis (e.g. streptokinase) is required to improve RV function by decreasing elevated pulmonary arterial pressure (26).

In patients without haemodynamic compromise clinical benefits of thrombolysis are controversial. The PEITHO trial, a multicentre randomized study, compared thrombolysis plus heparin against placebo plus heparin in patients with intermediate-risk PE (54). The all-cause 7-day mortality was low in both groups and not significantly different. The fibrinolytic therapy reduced significantly the rate of hemodynamic collapse, but increased the risk of major haemorrhage and stroke. A central problem of risk stratification is how to correctly identify patients in this subgroup. The present work aims to contribute to this problem.

In the case of absolute contraindications for thrombolysis or after its unsuccessful application, operative embolectomy (55) or percutaneous catheter procedures (56) are alternatives. In the long-term therapy and secondary prophylaxis vitamin K antagonists such as phenprocoumon or even newer anticoagulants (e.g. rivaroxaban, edoxaban, dabigatran) are

recommended (26). The duration of treatment depends on the risk profile of the patient and should be at least 3 months to prevent recurrences (26).

1.2 Risk Stratification

To avert potentially lethal outcomes and to provide adequate therapy for patients, it is of paramount importance to estimate the patient's risk. McIntyre and Sasahara showed for the first time that the prognosis of patients with PE mainly depends on the presence and extent of RVD (57). Therefore, in addition to the hemodynamic status, the right heart function has to be evaluated. This requires the detection and combined consideration of clinical, echocardiographic and laboratory markers (45).

1.2.1 Clinical Presentation

The classification of clinical presentation is based on systolic blood pressure (Table 1.2). The presence of a shock or hypotension indicates a high risk of early death and requires immediately re-channeling procedures. Persistent hypotension is defined in the present guidelines with systolic blood pressure < 90 mmHg. Lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia or sepsis. However, the majority of patients with PE are normotensive and the risk of mortality is classified as intermediate or low.

1.2.2 Imaging Techniques

For risk assessment, echocardiography and CT are suitable. Echocardiographic findings, which are indicating RV dysfunction, have been reported in more than 25% of patients with PE (44). These findings are independent predictors of an adverse outcome (58). Additionally, in normotensive and haemodynamically stable patients with PE, echocardiographic assessment of the morphology and function of the RV may help in prognostic stratification. Echocardiographic findings used to risk stratify patients with PE include RV dilation, an increased RV–LV diameter ratio, hypokinesia of the free RV wall, increased velocity of the jet of tricuspid regurgitation, decreased tricuspid annulus plane systolic excursion, or combinations of the above. Meta-analyses have shown that RV dysfunction in echocardiography is associated with an increased risk of short-term mortality in haemodynamically stable PE, but its overall positive predictive value is low (59, 60) .

In MDCT angiography, in particular the RV/LV ratio is meaningful; values greater than 0.9 in the reconstructed 4-chamber view are associated with a 5-fold increased risk of (49). The

prognostic value of an enlarged RV on CT angiography was confirmed by a prospective multicentre cohort study (61). However, statements about the dynamic RV function are difficult.

1.2.3 Biomarkers

Cardiac biomarkers represent a clinically extensively researched area for improving risk stratification in PE. Specifically, these are mainly TnT / I and BNP, its molecular precursor (NT) proBNP and, to a limited extent, other laboratory parameters such as myoglobin or D-dimers. H-FABP used in diagnostics of acute coronary syndrom was first reported in patients with PE and identified as a prognostic marker (8, 62, 63). For detecting myocardial injury creatinine kinase isoenzyme MB (CK-MB) is an additional important biomarker, which is used especially in detecting acute myocardial infarction.

Natriuretic Peptides

BNP and NT-proBNP are established in cardiac heart failure diagnostics (64). The potential of PE risk stratification is derived from its release mechanism. The stimulus for gene induction and expression, synthesis and secretion of BNP is the expansion of ventricular cardiomyocytes in RV dilatation (65). There is no intracellular storage so that several hours may elapse between the onset of RVD and peptide release, which required repeated testing. Although increased plasma levels correlate with the presence of RVD, the positive predictive value (PPV) is low (66). Due to its high negative predictive value (NPV) of more than 99%, its use is mainly to exclude potentially risk courses (5, 67). On the other hand, in a prospective, multicentre cohort study, NT-proBNP plasma concentrations of 600 pg/mL were identified as the optimal cut-off value for the identification of increased risk (68).

Cardiac Troponins

Cardiac troponins (TnT / I) represent the current gold standard in diagnostics of acute coronary syndrom and are also used in PE to estimate the prognosis (26). They are sensitive indicators of damage to the cardiomyocytes and show as a necrosis marker in PE a microinfarction of the right ventricular subendocardial tissue. Since TnT / I values only increase after about six hours, they have to be determined several times. Elevated plasma levels are found in 11% - 50% of PE and correlate with the extent of RVD (69). The NPV is over 97%, while the PPV is 12% - 44% (66).

The role of TnT / I in risk stratification is currently controversial. A meta-analysis from Becattini et al. with 1985 patients concluded that increased TnT / I levels may identify those patients (including the Intermediate Risks Group) who are at risk of complicated clinical course or death (70). However, Jiménez et al. have shown in a meta-analysis with 1366 normotensive patients, that increased troponin levels within the intermediate risk group do not predict an increased mortality (71). Further studies confirmed this result (11, 72).

Creatinine kinase isoenzyme MB (CK-MB)

Creatinine kinase isoenzyme MB is an important biomarker for detecting myocardial injury (73). Many studies have reported that CK-MB is associated with in-hospital and long-term mortality in patients with acute coronary syndrome (ACS) (74-76). In a large study, Chin et al. [30] evaluated 16,009 patients with ST elevation myocardial infarction (STEMI) and 26,854 patients with non-STEMI and they found that peak CK-MB level was an independent predictor of inhospital mortality.

Stein et al investigate the potential prognostic value of CK-MB in normotensive patients with PE. Although their findings were statistically not significant, CK-MB tended to be a stronger predictor of death than cTnT and the combination of CK-MB, cTnT and echocardiography seemed particularly indicative (12).

In patients with acute PE treated with lysis Bozbay et al. (77) showed that a CK-MB value of more than 31.5 U/L yielded a sensitivity of 86.7% and specificity of 83.5% for predicting in-hospital mortality.

1.3 Methodological Basics

1.3.1 Molecular Characteristics, Occurrence and Function of H-FABP

The fatty acid binding proteins (FABPs), discovered in a study of intestinal fat absorption, have been firstly described by Ockner et al. (78). It is a protein family that has a high affinity for non-covalent binding of fatty acids in the cytosol and transports fatty acids as an intracellular counterpart to albumin (79). Since fatty acids in the body ubiquitously serve as an energy source, FABPs are widely distributed in different tissues and thus an integral part of the fatty acid metabolism. They modulate specific catabolic and anabolic enzymes of lipid metabolism via their transport function, regulate the cellular fatty acid level (steady state), which influence the structural integrity of lipid membranes, and are also important for gene regulation and expression (80). The highest levels of FABPs in humans are detected in liver and heart, in which the human heart receives approximately 50% - 80% of its energy from lipid oxidation

accounting for 10% of the total metabolic rate of the fatty acid (81). At present, 9 tissue-specific FABPs are known, which are specified in the nomenclature with an additional letter (Heart, H-FABP; Liver, L-FABP; Intestinal, I-FABP; Adipocyte, A-FABP; Epidermal, E-FABP; Ileal, Il-FABP; Brain, B-FABP; Myelin, M-FABP; Testis, T-FABP) (82). The H-FABP synthesis occurs mainly in cardiomyocytes, but to a lesser extent also in skeletal muscle, kidney distal tubule cells, some portions of the brain, and the lactating mamma and placenta (83). The elimination occurs by kidney. The molecular characteristics are depicted in table 1.5 (84). H-FABP is a stable protein that survives multiple freeze and thaw cycles without loss of immunoreactivity (85).

Table 1. 5 Molecular characteristics of H-FABP

	Characteristics	**Structure**
Classification	Lipid-binding protein	
Molecular weight	14748.00 Da	
Number of amino acids	132	
Secondary structure	15% α-helix 53% β-leaflet (10 Stränge)	
Gene locus	1p32-p33	
Occurence	esp. heart muscle	

1.3.2 Clinical Significance of H-FABP

While H-FABP is a strict intracellular protein, the plasma concentration of H-FABP measured in healthy individuals is less than 5 ng/ml. This is probably caused by stressed, microtraumatized skeletal muscles (83). Plasma levels vary according to gender (greater muscle mass in men) and age (decreased renal clearance). When combined with clinical symptoms, measured values above 6 ng/ml are considered pathological (83). Due to the low molecular weight and the unbound localization in the cytoplasm, a rapid release into the plasma occurs after myocardial ischemia. The high intracellular, but low extracellular concentration leads to a steep increase in concentration, which is detectable already 20 minutes after injury and whose maximum is three to four hours. Complete renal elimination occurs in normal renal function within 24 to 36 hours (86).

H-FABP in Heart Diseases

Since the 1990s, H-FABP assays have been successfully used in early diagnosis in suspected acute coronary syndrome. It is superior to the other plasma markers like myoglobin, creatine kinase isoenzyme MB (CK-MB), and TnT in terms of sensitivity and specificity in the time window up to 6 hours after injury (8, 86). At the same time, normalization within 36 hours offers the opportunity to diagnose any reinfarction that would be obscured by the kinetics of the other markers (83). H-FABP could also be of importance in left heart failure (87) and chronic thromboembolic pulmonary hypertension (88).

H-FABP in Pulmonary Embolism

Due to promising results in the risk stratification of patients with acute coronary syndrom, H-FABP was also of interest for assessing the prognosis in PE. The first related study was published by Kaczynska et al. (63), further studies followed (11, 72).

1.3.3 Right Ventricular Anatomy and Echocardiographic Assessment

The RV conforms to the ellipsoid-shaped LV in a crescent shape with complex geometry and is anatomically-functional structered in two parts, the inflow and outflow tract (89). The complex anatomy and the fact that the main task of the RV is - in contrast to the pressure-generating LV - volume transport, is reflected in the different contraction mechanism. While the LV predominantly contracts via a concentric-rotatory movement, the RV “pushes” the blood further into the pulmonary circulation, mainly via a shortening of the length with a rotational component. However, volume transport is poorly quantifiable by echocardiography, so that the RV function could be assessed almost exclusively on a qualitative basis only (13). For better assessability, echocardiographic parameters such as the TAPSE or mTDI are increasingly being used.

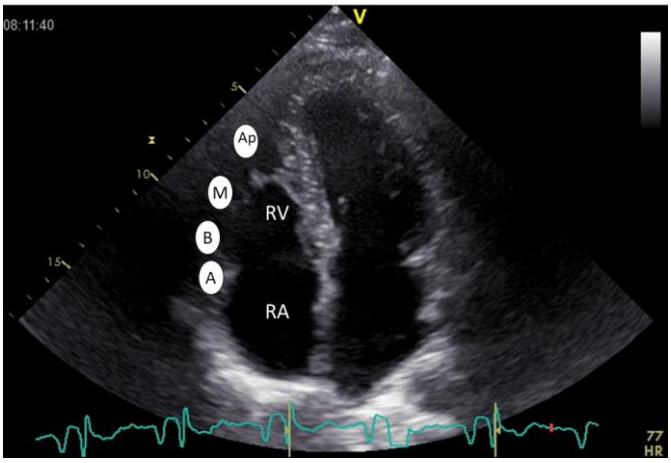

Figure 1. 3 Echocardiographic views of the right ventricle (RV).
The RV viewed from apical four-chamber view with the right atrium (RA). A, annular level; B, basal level; M, mid level; Ap, apical level.

Selected Parameters for Diagnosis of Acute Right Ventricular Dysfunction

Table 1.6 gives an overview of specific echocardiographic findings that can be evaluated in the transthoracic examination, which often can but do not have to occur on the RV under acute pressure (89, 90).

Table 1. 6 Typical echocardiographic findings in acute pressure overload of the RV (89, 90)

	Explanation	**Method**	**Standard Value**
Paradoxic septal movement	Systolic turn of the septum towards LV, impairment of LV filling	2D, M-Mode	negative
TAPSE	Distance of tricuspid annulus movement from end diastole to end-systole, correlation with RV ejection fraction	M-Mode	25,5 ± 4,7 mm
McConnell sign	Hypokinesia of the middle free RV wall with normal contraction of the RV apex	2D	negative
Increased right ventricular systolic pressure (RVSP)	Quantifying the pressure load of the RV	Bernoulli's equation	≤ 35mmHg
RV dilatation	Extension of the end-diastolic RV diameter	2D	≤ 30mm
RA dilatation	Extension of the end-systolic RA diameter	2D	≤ 40mm
Tricuspid regurgitation	Extension of the tricuspid annulus in RA and RV dilation leads to incapacity	colour Doppler, CW Doppler	negative

2D – two dimensional, CW – continuous wave, M-mode – motion mode

1.3.4 Myocardial Tissue Doppler Imaging

The technique is based on the principles of Doppler echocardiography. Signals are analyzed that are not derived from cellular blood components (conventional Doppler), but from the surrounding tissue. The tissue signals are higher in amplitude (about 100 times) and slower (less than 10 cm/s) compared to blood. In conventional Doppler, the slower, tissue-specific signals are filtered out. To measure selectively tissue movements, opposite frequency and amplitude filters were used and the overall gain is reduced. The representation can be color-coded in 2D mode or as pulsed-wave (PW) Doppler (91). The mTDI thus allows a statement about the systolic and diastolic function via the examination of regional myocardial velocities and may

show abnormalities earlier than affecting global function. The mTDI thus provides information on the systolic and diastolic function through the examination of regional myocardial velocities and may show abnormalities before impairment of global function earlier (91).

Application

The PW Doppler beam is placed in the myocardium section of interest. The velocity of tissue movement is represented as a function of time. In the measured myocardial movements, the systolic (S ') and the early (E') and late-diastolic (A ') peak velocities can be distinguished. Figure 1.3 illustrates the derivation and representation schematically. To avoid axial and resulting velocity deviations, mTDI should be performed apically, since the position of the apex is relatively fixed during the contraction cycle and the movement in the frontal plane is approximately parallel to the measurement point. The results can be reproduced between different examiners (92).

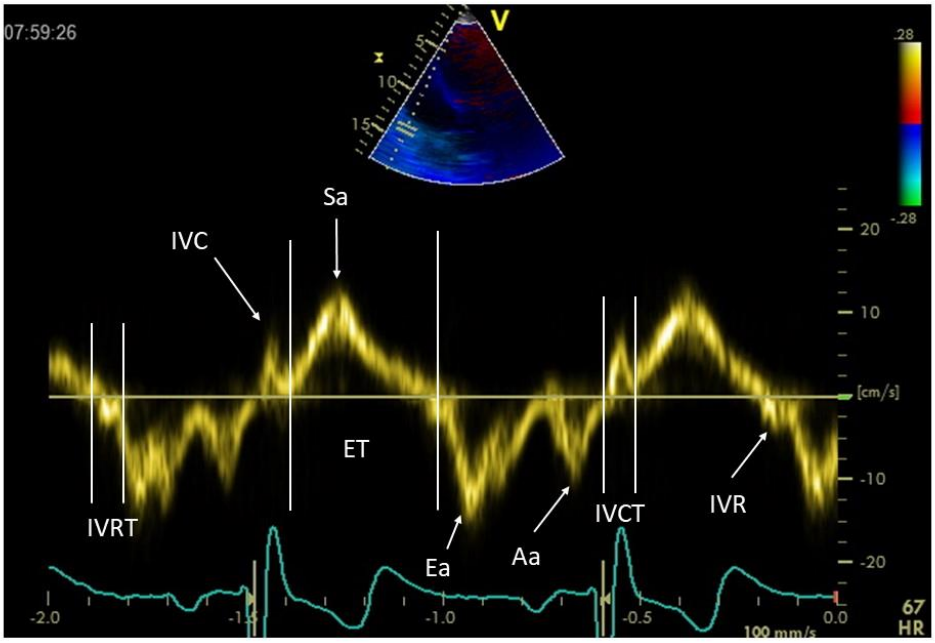

Figure 1. 4 mTDI of right ventricle, normal findings.
Sa = S’ 14 cm/s, Ea = E’ 16 cm/s, Aa = A’ 10 cm/s (different nomenclatures exist); further referred to: ejection (ET), (isovolumic) relaxation (IVRT) and contraction time (IVCT) as well as relaxation and contraction rates (IVR, IVC)

The standard values of the lateral tricuspid ring are 14.5 ± 2.6 cm / s for S ', 14.1 ± 3.7 cm / s for E' and 16.6 ± 5.5 cm / s for A ' (89).

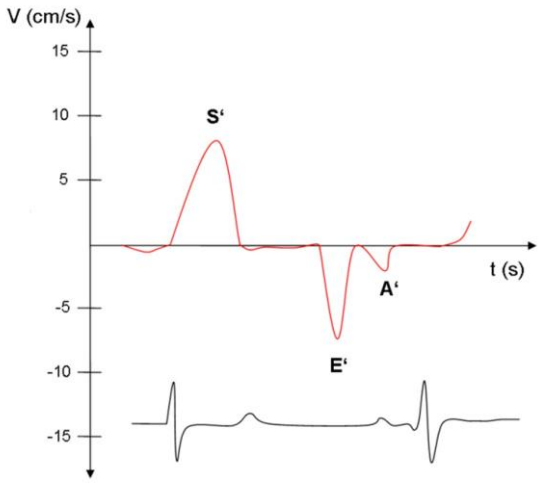

Figure 1. 5 Myocardial velocities in mTDI by means of PW-Doppler (schematic).
S 'is the peak velocity of myocardial shortening during the (S) ystole. This is followed by the myocardial movement, which results from the premature ([E] arly) filling of the ventricle (peak velocity E '). Directly after the P-wave in the ECG, the (A) triale contraction causes (= late-diastolic) myocardial movement with the peak velocity A '. Positive deflections are caused by motion away from the transducer, negative by movement towards the transducer. Isovolemic contraction and relaxation phases are not indicated.

2 Aim and Hypothesis

Currently, for the group of normotensive patients with RVD (intermediate mortality risk) there are only limited satisfactory therapy recommendations (26). There may be a subgroup of "normotensive high-risk patients" with a significantly higher mortality risk. The question is whether and which of these patients could benefit from thrombolysis. In view of the doubts regarding the suitability of troponin as a prognostic indicator (71), the key question for the identification of these patients is yet unanswered. Furthermore, TAPSE and mTDI are emerging prognostic indicators in normotensive patients with PE.

The objective of the study is to assess the potential role for prognostic value (PE-related mortality within 30 days) of CK-MB and TDI in echocardiography in view of both new (H-FABP) and established (cTnT/I, RVD) risk markers. CK-MB and additional echocardiografic parameters like TDI have not been studied in detail for risk assessment in patients with intermediate risk pulmonary embolism.

The thesis has two hypotheses which are observational in nature:

- Heart-type Fatty Acid Binding Protein and Creatine Kinase isoenzyme MB are better prognostic factors than cardiac biomarkers troponin T, troponin I and CK, in patients with pulmonary embolism and intermediate risk of death within 30 days

- In patients with intermediate risk pulmonary embolism, advanced echocardiografic parameters (tissue Doppler imaging) provide a better prognostic value than well-established parameters (RV diameter, RV/LV-index, paradoxical septum movement, McConnell sign, right ventricular ejection fraction, Tricuspid Annular Plane Systolic Excursion).

3 Methods

3.1 Study Design

Between 2005 and 2010 consecutive patients diagnosed and treated with pulmonary artery embolism at the Heart Center Dresden (University Hospital of the Faculty of Medicine Carl Gustav Carus of the Dresden University of Technology) and with a systolic blood pressure above 90 mmHg at admission were included. There was a comprehensive education of all patients about the type, extent and evaluation of this study designed as an observational study. The necessary measurements (blood collection and echocardiographic examination) were integrated into the normal routine diagnostic procedure, so no additional procedures or examinations were needed. The results of the investigation did not at any time determine the further diagnostic-therapeutic procedure and treating physicians had no knowledge of the test results. The study protocol was approved by the local ethical committee from Dresden University of Technology.

Detection of Pulmonary Embolism

Diagnosis assurance was performed by using MDCT and ventilation–perfusion scintigraphy, taking into account clinical probability (46) and D-dimer levels. In unstable circulatory situation and resulting transport inability the diagnosis was made by bedside transthoracic echocardiography and compression sonography of the leg veins (diagnosis of DVT).

Blood Collection and Laboratory Parameters

The study protocol provided for blood sampling within 6 hours of hospital admission or diagnosis, which could be ensured by integration into the routine reception lab. In addition to the laboratory routine, an H-FABP quick test was used in all cases (see 2.2). After centrifugation[1] and pipetting off the plasma, the samples were frozen at -80 °C for later quantitative collection and disposed of after measurement. The routine laboratory also included the determination of TnI[2], creatine kinase (CK) and CK-MB[3], D-dimers[4], creatinine, urea,

[1] Heraeus Megafuge R, 4000 rpm for 10 minutes at 4°C
[2] Chemiluminescent immunoassay of Ortho-Clinical Diagnostics Inc, upper reference 0.08 ng ml
[3] Immunoinhibition assay, Hitachi analyzer (Trinity PLC, Bray, Ireland), upper reference 0.4 µkat/l
[4] Latex agglutination test, Hitachi analyzer (Trinity PLC, Bray, Ireland), upper reference value 0.25 µg/ml

glomerular filtration rate (GFR)[5] (93), small blood counts, glucose, electrolytes, transaminases, coagulation parameters and thyroid stimulating hormone (TSH).

Transthoracic Echocardiography

After diagnosis, the study protocol provided for the implementation of transthoracic echocardiography (parameters and technique description see 2.3.1) within 3 hours. The number of examiners was limited to experienced users who had no knowledge about the H-FABP test result.

Inclusion / Exclusion Criteria

Patients aged 18 and over were included in the study if a diagnosed PE was the cause of the acute symptoms and if the systolic blood pressure was above 90 mmHg. After informed consent was given, patients were included in the study. Exclusion from the study happened in case of cardiogenic shock, haemodynamic instability, catecholamine administration or systolic blood pressure below 90 mmHg, or concomitantly diseases such as acute coronary syndrome, decompensated cardiac failure, pulmonary hypertension, severe respiratory diseases such as chronic obstructive pulmonary disease, severe chronic renal insufficiency IV[6] (79, 94), or severe muscle disease.

Outcomes

The definition of the primary endpoint included the lethal course within 30 days of hospital admission (30-day lethality).

The secondary endpoint was a complicated clinical course within 30 days. This included the following events: successful resuscitation; cardiogenic shock or hypotension[7]; use of catecholamines for circulatory stabilization; therapy escalation in the form of thrombolysis, embolectomy, intubation and mechanical ventilation or extracorporeal membrane oxygenation.

3.2 H-FABP Determination

Qualitatively

The commercially available quick test CardioDetect® med from Rennesens GmbH was used for the qualitative determination of H-FABP (Table 2.1). This test is based on a non-competitive

[5] calculated according to the "Modification of Diet in Renal Disease" formula
[6] GFR <30ml/min
[7] systolic blood pressure <90mmHg or drop by at least 40mmHg over 15min

immunoassay ("sandwich" method) with two monoclonal antibodies, where the gold-labeled primary monoclonal antibody released from the matrix by the added sample fluid forms an intermediate complex with H-FABP and is transported through the detection zone. At the position designated as "H-FABP", the intermediate-complex forms a sandwich complex with the second monoclonal antibody bound there. When the threshold concentration of 7 ng / ml in the sample is exceeded, the sandwich complex appears as a violet band (test positive). If the concentration falls below 7 ng/ml, insufficient amounts of intermediate and secondary complexes are formed and the band does not appear (test negative).

Table 3. 1 Properties of the H-FABP quick test (95)

	Characteristics
Threshold 7	7 ng / ml
Sample material	whole blood, serum, plasma
Sample amount	80-100 µl
Time window	20 min to 1 day
Test duration	15 min
Sensitivity	69.1%

3.3 Echocardiographic Examination

3.3.1 Conventional Echocardiography of the Right Ventricle

For the standardized transthoracic echocardiographic examination, the device "I33" (type 2D Echo) from Philips was used. The examination was done at the bedside in left lateral position with synchronous ECG derivation. The aim was, in addition to the evaluation of LV and global pump function, the determination of various RV parameters.

The quantitative measurement of RV and RA diameters as well as the qualitative assessment of the RV function was performed in B(rightness) mode in the apical 4-chamber view. The RV pressure ratios and pumping function were assessed visually by the examiner. The RV ejection fraction was determined by the modified Simpson method (96) and defined a value <45% as a moderate to severe restriction (97). Furthermore, the presence of a paradoxical septal movement or a positive McConnell sign was of interest.

To calculate the RV / LV ratio of the cross-sectional area and the eccentricity index, the measurement of the RV and LV diameters occurred in the M(otion) mode. In the next step, the TAPSE was determined by placing the signal over the lateral tricuspid valve annulus. The

repeated septal examination in the short parasternal axis served to verify or exclude a paradoxical movement.

Using the CW (continous wave) Doppler, quantification of concomitant tricuspid regurgitation (TR) was performed. By means of the modified Bernoulli equation[8], the TR signal was used to estimate the pulmonary artery pressure and above that the pressure load of the RV in the systole (RVSP).

Echocardiographic Evidence of RV Dysfunction

Echocardiographic recording of RVD is one of the cornerstones of risk stratification algorithms in addition to laboratory testing and suggests an increased mortality risk in normotensive patients (26, 58). The echocardiographic diagnosis was defined according to Konstantinides (69):

- Hypokinesia of the free RV wall
- RV dilation, end diastolic diameter (EDD)> 30mm or RVEDD / LVEDD ≥ 0.9
- Paradoxical septal movement
- Increased RVSP and extension or congestion of the inferior vena cava.

Since a generally accepted definition does not yet exist, only patients with a completely normal echo (and normal laboratory parameters) have been classified as low risk based on current guidelines (26).

3.3.2 Myocardial Tissue Doppler Imaging

The measurement of the mTDI parameters was carried out as part of the transthoracic echocardiographic examination by apical placement of the PW Doppler beam in the to be examined myocardium section. The detected velocities S ', E' and A 'of the lateral tricuspid ring are well-studied and validated reference values are available (see 1.3.4), where S' correlates very well with the systolic RV function (89, 92).

3.4 Statistics

For data collection, a pseudonymized database was used. The statistical analysis was done with SPSS (Version 15.0, IBM, USA) after coding of binary and ordinal scaled variables. The

[8] $P_{PA(syst)}=4 \times V^2_{max(TI)}+ P_{RA}$, the RA pressure is represented by the breath-modulated width of the V. cava inferior

normal distribution test of continuous variables was done according to the sample size using the Lilliefor corrected Kolmogorov-Smirnov test or the Shapiro-Wilks test.

Descriptive statistical values, unless otherwise indicated, are mean ± standard deviation. In the case of deviation from the normal distribution, the median is given with the associated 0.25 and 0.75 quantiles (lower-upper quartile).

The Student's t-test was used as a statistical significance test to verify the difference between two independent samples for normally distributed data, and the nonparametric Mann-Whitney U test for testing non-normalized data.

For the overwhelming majority of the various analyses, the dichotomization and the presentation of these categorical variables in four-field panel was carried out. Statistical differences were analyzed using the Pearson χ^2 test or Fisher's exact test when more than 25% of the cells contained expected frequencies less than 5. Depending on the scale level, the coefficients are given according to Pearson, Spearman or the φ coefficient as correlation measures.

The Kaplan-Meyer analyses show group differences in cumulative survival. For this purpose, the prognostic parameters TnI and H-FABP were combined into 4 groups depending on the positive (+) or negative (-) test result (TnI + / H-FABP +, TnI + / H-FABP-, TnI- / H-FABP +, TnI- / H-FABP-) and by log-rank test for significant differences.

All P values given in the present study are determined by 2-sided tests and considered to be statistically significant at $P < 0.05$. High-significance results that SPSS outputs with the value 0.000 are specified in the work as <0.001. For reasons of clarity, values with $p > 0.1$ are replaced by "not significant" (ns).

Logistic Regression Analysis

Regarding their prognostic value, the biochemical and clinical parameters were subjected to a univariate and multivariate logistic regression analysis. The univariate logistic regression analysis identifies possible prognostic factors with regard to the outcomes (= dependent variables) through their individual examination. The classification as a significant potential predictor applies to parameters whose calculated 95% confidence interval (95% CI) of the odds ratio (OR) does not contain the value "1" and whose p-value in the likelihood ratio test is less than 0.05. Subsequently, the stepwise investigation of the factors identified was carried out with a multivariate logistic regression model in order to uncover mutual influences of the covariate or prediction parameters.

Receiver Operating Characteristic (ROC) Analysis

To determine the reliability and as a measure of the selectivity of the diagnostic parameters, ROC analyzes were performed and the area under the curve (AUC) was determined. Selectivity is when the AUC is greater than 0.5 and the result is statistically significant ($P < 0.05$). Based on the coordinates of the curves, it was also possible to determine threshold values for the parameters investigated at the points of the best possible sensitivity and specificity. The analyzes and comparisons of the ROC curves were done with Medcalc (version 12.2.1, MedCalc Software, Belgium).

4 Results

4.1 Patient Characteristics

For this study 176 consecutive patients were screened. Eight patients were excluded due to comorbidities, which included acute myocardial infarction (n = 2), exacerbated COPD (n = 3), acute heart failure with right heart decompensation (n = 2) and a mediastinal tumor (n = 1). Another seven patients were excluded because of systolic RR values lower than 90 mmHg, limited GFR or incomplete laboratory values (Figure 4.1).

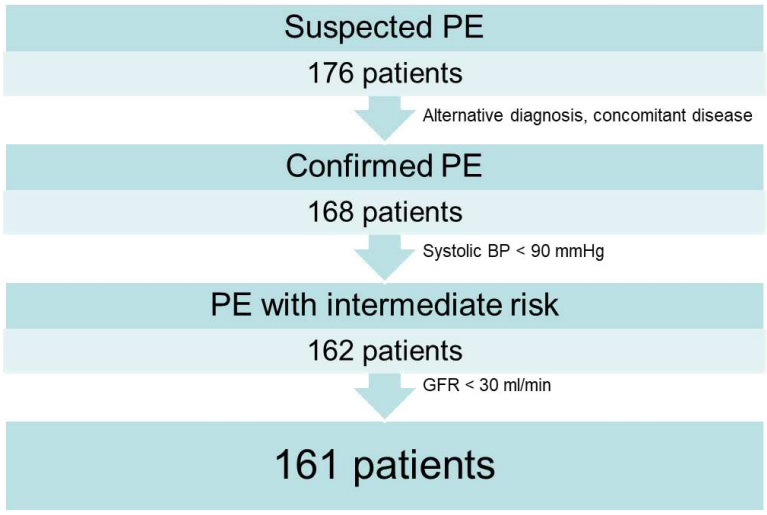

Figure 4. 1 Number of patients

4.1.1 Demographic data

Table 4.1 provides an overview of the study population in terms of age, sex, PE-related parameters and risk factors, as well as comorbidities and renal function.

The mean age was 69 ± 13.5 years and women (n = 90; 55.9%) were more represented than men (n = 71; 44.1%). In 70% of patients, DVT was found to be the cause of PE, and in around 32% of patients a history of classic risk factors such as immobilization was found. More than 75% of the patients had arterial hypertension, about 50% had hyperlipidemia and about 29% had type 2 diabetes mellitus. An underlying malignancy or history of malignant disease was found in 18% of patients. The average body mass index (BMI) was 29.2 ± 5.7 kg/m^2, and average values of creatinine and urea were 100 µmol/l (IQR 83-129) and 6.8 mmol/l (IQR 5.5-9.9) respectively. The average length of hospital stay was 8.7 ± 4.7 days (Table 4.1).

Table 4. 1 Baseline characteristics of the subjects

Baseline Characteristics	**N=161**
Age (years); mean±SD	69 ± 13.5
Gender (females); N (%)	90 (55.9)
sPESI ≥ 1; N (%)	71 (44)
Acute onset (<3 days); N (%)	61 (37.9)
DVT; N (%)	113 (70.2)
Cancer; N (%)	29 (18.1)
Hypertension; N (%)	124 (77)
Diabetes mellitus; N (%)	46 (28.6)
HLP; N (%)	79 (49.1)
Smoking; N (%)	14 (8.7)
BMI (kg/m²); mean±SD	29.2 ± 5.7
Creatinine (µmol/l); median (IQR)	100 (83-129)
Urea (mmol/l); median (IQR)	6.8 (5.5-9.9)
GFR (ml/min); mean±SD	56 ±19

4.1.2 Endpoints

Primary endpoint

Overall, 16 of 161 patients died, after 4.3 ± 3.8 days from admission. This equates to a 30-day mortality rate of 9.9%. Table 3.2 gives an overview of demographic data of deceased and survivors.

Deceased patients tended to be younger and male, although this observation was not statistically significant. There was no significant difference between both groups regard to a sPESI ≥ 1. Strikingly the symptoms of the deceased were significantly more frequently manifested acutely. In addition, malignant tumors and, more rarely, hyperlipidemia were found to be significantly more frequent in deceased patients. Renal function was significantly more decreased in deceased patients.

Table 4. 2 Baseline characteristics in relation to 30-day-mortality

Primary endpoint	**Deceased patients (n=16)**	**Survived patients (n=145)**	**p**
Age (years); mean±SD	63.0 ± 17.0	69.5 ± 13.0	0.313
Gender (females); N (%)	7 (43.7)	83 (57.2)	0.302
Acute onset (<3 days); N (%)	12 (75.0)	49 (33.8)	0.001
sPESI (≥1); N (%)	9 (56.3)	62 (42.8)	0.302
DVT; N (%)	10 (62.5)	103 (71.0)	0.566
Cancer; N (%)	6 (37.5)	23 (15.9)	0.044
Hypertension; N (%)	10 (62.5)	114 (78.6)	0.206
Diabetes mellitus; N (%)	8 (50.0)	38 (26.2)	0.076
HLP; N (%)	4 (25.0)	75 (51.7%)	0.042
Smoking; N (%)	1 (6.3)	14 (9.7%)	1.000
BMI (kg/m²); mean±SD	30.6 ± 7.9	291 ± 54	0.741
Creatinine (µmol/l); median (IQR)	144 (91-219)	98 (82-122)	0.007
Urea (mmol/l); median (IQR)	7.6 (5.2-21.7)	6.8 (4.2-9.5)	0.267
GFR (ml/min); mean±SD	43 ±12	58 ± 18	0.003

Secondary endpoint

Of the 145 surviving patients, 25 patients (17.2%) had a complicated clinical course. 2 (8%) of them were reanimated, 18 (72%) lysed, 12 (48%) received catecholamines and one patient (4%) was embolectomized. Table 4.3 shows that patients differ only in the distribution of malignancies significantly. Furthermore, patients with nicotine abuse tended to have complications, but the difference was not significant (P = 0.068).

Table 4. 3 Baseline characteristics in relation to complicated clinical course

Secondary endpoint	complicated clinical course (n=25)	non-complicated clinical course (n=120)	P
Age (years); mean±SD	67.8 ± 12.5	69.8 ± 13.1	0.689
Gender (females); N (%)	17 (68.0)	66 (55.0)	0.185
Acute onset (<3 days); N (%)	9 (36.0)	40 (33.3)	0.832
sPESI (≥1); N (%)	14 (56.0)	48 (40.0)	0.192
DVT; N (%)	18 (72.0)	85 (70.8)	0.829
Cancer; N (%)	0 (0.0)	23 (19.2)	0.011
Hypertension; N (%)	20 (80.0)	94 (78.3)	0.700
Diabetes mellitus; N (%)	5 (20.0)	33 (27.5)	0.302
HLP; N (%)	14 (56.0)	61 (50.8)	0.451
Smoking; N (%)	5 (20.0)	9 (7.5)	0.068
BMI (kg/m²); mean±SD	27.5 ± 3.9	29.4 ± 5.7	0.083
Creatinine (µmol/l); median (IQR)	97 (83-113)	101 (83-130)	0.371
Urea (mmol/l); median (IQR)	7.1 (5.0-10.7)	6.8 (5.3-9.8)	0.734
GFR (ml/min); mean±SD	58.5 ± 16.3	57.7 ± 18.3	0.393

4.1.3 Risk profile

Clinical parameters

The clinical parameters of systolic blood pressure, heart rate and oxygen saturation are plotted against the endpoints in Table 4.4. Patients who reached an endpoint had significantly lower systolic blood pressure and significantly higher heart rates. Oxygen saturation was only significantly different in patients who had a complicated clinical course.

Table 4. 4 Clinical parameters related to the endpoints

30-day-mortality			
	positive (n=16)	negative (n=145)	P
RR_{sys} (mmHg); mean±SD	103±11	135±22	0.001
HR (min^{-1}); mean±SD	110±25	90±18	0.009
SaO_2 (%); mean±SD	91±7.6	92±4.9	ns

Complicated clinical course			
	positive (n=25)	negative (n=120)	P
RR_{sys} (mmHg); mean±SD	124±23	138±21	0.005
HR (min^{-1}); mean±SD	98±16	88±18	0.018
SaO_2 (%); mean±SD	90±5.6	93±4.5	0.037

Labratory parameters

Tables 4.5 and 4.6 illustrate the differences in the laboratory parameters between the individual groups. All cardiac biomarkers, besides D-dimers, were significantly increased in deceased patients compared to survivors (Tabl. 4.5). In patients with a complicated clinical course, only the H-FABP rapid test was significantly more positive (Table 4.6).

Table 4. 5 Laboratory values related to the 30-day-mortality

	Deceased patients (n=16)	**Survived patients (n=145)**	p
H-FABP (positive); N (%)	15 (93.8)	11 (7.6)	<0.001
TnI (positive > 0.08ng/ml); N (%)	13 (81.3)	53 (36.6)	0.001
TnI (ng/ml); median (IQR)	0.21 (0.03-0.72)	0.04 (0.01-0.68)	0.001
CK (positive > 2.85 µkat/L); N (%)	9 (56.3)	25 (17.2)	0.002
CK (µkat/l); median (IQR)	3.01 (1.10-25.13)	1.27 (0.86-2.11)	<0.001
CK-MB (positive > 0.4 µkat/L); N (%)	14 (87.5)	27 (18.6)	<0.001
CK-MB (µkat/l); median (IQR)	1.44 (0.38-4.02)	0.22 (0.15-0.31)	<0.001
D-dimere (µg/ml); median (IQR)	3.48 (2.17-8.03)	2.71 (1.87-6.96)	0.365

Table 4. 6 Laboratory values related to complicated clinical course

	complicated clinical course (n=25)	**non-complicated clinical course (n=120)**	p
H-FABP (positive); N (%)	7 (28.0)	4 (3.3)	<0.001
TnI (positive > 0.08ng/ml); N (%)	10 (40.0)	43 (35.8)	0.646
TnI (ng/ml); median (IQR)	0.05 (0.01-0.02)	0.04 (0.01-0.10)	0.825
CK (positive > 2.85 µkat/L); N (%)	7 (28.0)	28 (23.3)	0.556
CK (µkat/l); median (IQR)	1.35 (0.34-1.29)	1.28 (0.89-2.44)	0.256
CK-MB (positive > 0.4 µkat/L); N (%)	3 (12.0)	36 (30.0)	0.132
CK-MB (µkat/l); median (IQR)	0.37 (0.15-2.54)	0.22 (0.15-0.40)	0.388
D-dimere (µg/ml); median (IQR)	2.69 (2.39-16.40)	2.73 (2.06-7.73)	0.403

Echocardiography

Deceased patients had significantly enlarged RV and significantly smaller LV diameters. Accordingly, the RV / LV and LV / RV indices differ at P <0.001 (Table 4.7). A paradoxical septal movement was found to be significantly more frequent in deceased patients (P = 0.001). The presence of a McConnell sign was also significantly different between patients who died and those who survived (P = 0.044). There were no significant differences between the groups for the ventricular geometry (sphericity index, eccentricity index), RVSP level, tricuspid incidence, and LV function.

Among the specific RV parameters, only the visually estimated RV ejection function and the TAPSE showed highly significant differences. Thus, the RV ejection function was moderate in deceased patients and only slightly decreased in survivors (P <0.001). The average TAPSE values in deceased patients were 5 mm below those of surviving patients (P <0.001). Although the mTDI parameters tended to be reduced, the differences did not reach statistical significance (Table 4.7).

Table 4. 7 Echocardiographic parameter related to 30 day-mortality

	Deceased patients (n=16)	**Survived patients (n=145)**	P
Enlarged RV; N (%)	16 (100)	112 (77.2)	0.044
RV-diameter (mm); mean±SD	41.3 ± 4.7	36.5 ± 6.0	0.004
LV-diameter (mm); mean±SD	38.2 ± 4.3	43.6 ± 7.0	0.003
LV/RV ratio; mean±SD	0.94 ± 0.17	1.24 ± 0.33	<0.001
RV/LV ratio; mean±SD	1.09 ± 0.19	0.86 ± 0.21	<0.001
Sphericity index; mean±SD	1.77 ± 0.32	1.72 ± 0.47	0.805
Eccentricity index; mean±SD	1.55 ± 0.29	1.68 ± 0.47	0.716
PSM; N (%)	13 (81.3)	53 (36.6)	0.001
Positive McConnell-sign; N (%)	12 (75.0)	74 (51.0)	0.044
RVSP (mmHg); mean±SD	51 ± 14	55 ± 16	0.427
Restriction RV function; N (%)	15 (93.8)	106 (73.1)	
- non	1 (6.3)	39 (26.9)	
- low-grade	1 (6.3)	39 (26.9)	
- Moderate	8 (50.0)	55 (37.9)	<0.001
- high-grade	6 (37.5)	12 (8.3)	
Tricuspid regurgitation; N (%)	16 (100)	141 (97.2)	
-TI I°	2 (12.5)	63 (43.4)	
-TI II°	10 (62.5)	67 (46.2)	0.135
-TI III°	4 (25.0)	11 (7.6)	
LVEF (%); mean±SD	53 ± 10	55 ± 10	0.378
TAPSE (mm); mean±SD	13.7 ± 4.1	18.7 ± 4.8	<0.001
S' (cm/s); mean±SD	11.5 ± 4.9	12.0 ± 3.2	0.692
E' (cm/s); mean±SD	7.5 ± 5.0	9.2 ± 3.5	0.215
A' (cm/s); mean±SD	12.9 ± 4.5	13.6 ± 4.9	0.703

The results of the size indices of patients with complicated clinical history are similar to those of the deceased (Table 4.8). A positive McConnell sign was found to be highly significant in patients with complicated clinical course (P <0.001). Again, the groups are not significantly different in terms of ventricular geometry, average RVSP, and LVEF.

However, there was a significant difference in tricuspid regurgitation with (P = 0.031). 80 of patients with complicated clinical course had a regurgitation grade II-III. Almost 92 of patients without complications had a regurgitation grade I-II. RV function was also more limited in patients with complicated clinical course (P <0.001). The TAPSE values differed

significantly between the groups related to 30-day mortality and complicated course, as well as there was also a significant difference between the groups for S 'with p = 0.02 in primary and secondary endpoint.

Table 4. 8 Echocardiographic parameter related to complicated clinical course

	complicated clinical course (n=25)	**non-complicated clinical course (n=120)**	p
Enlarged RV; N (%)	25 (100)	87 (72.5)	0.003
RV-diameter (mm); mean±SD	39.4 ± 5.2	35.9 ± 6.0	0.008
LV-diameter (mm); mean±SD	40.3 ± 5.5	44.3 ± 7.1	0.005
LV/RV ratio; mean±SD	1.06 ± 0.24	1.28 ± 0.33	0.002
RV/LV ratio; mean±SD	0.98 ± 0.21	0.83 ± 0.21	0.001
Sphericity index; mean±SD	1.74 ± 0.37	1.71 ± 0.49	0.918
Eccentricity index; mean±SD	1.93 ± 0.37	1.57 ± 0.49	0.09
PSM; N (%)	12 (48.0)	41 (34.2)	0.507
Positive McConnell-sign; N (%)	22 (88.0)	52 (43.3)	<0.001
RVSP (mmHg); mean±SD	59 ± 16	54 ± 16	0.139
Restriction RV function; N (%)	25 (100.0)	81 (67.5)	
- non	0 (0.0)	39 (32.5)	
- low-grade	4 (16.0)	35 (29.2)	
- Moderate	16 (64.0)	39 (32.5)	<0.001
- high-grade	5 (20.0)	7 (5.8)	
Tricuspid regurgitation; N (%)	25 (100)	119 (99.2)	
-TI I°	5 (20.0)	58 (48.3)	
-TI II°	17 (68.0)	51 (42.5)	0.031
-TI III°	3 (12.0)	10 (8.3)	
LVEF (%); mean±SD	53 ± 11	56 ± 10	0.333
TAPSE (mm); mean±SD	13.9 ± 3.7	19.7 ± 4.5	<0.001
S' (cm/s); mean±SD	10.5 ± 3.2	12.4 ± 3.0	0.025
E' (cm/s); mean±SD	8.1 ± 2.6	9.4 ± 3.7	0.343
A' (cm/s); mean±SD	12.5 ± 5.7	13.8 ± 4.7	0.403

Ventricular size ratios are well described by the RV / LV index and are highly significantly different between the endpoint groups. Furthermore, the paradoxical septal movement was significantly more prevalent in deceased patients than in patients with a complicated clinical

course. Conversely, in patients with a complicated course it was significantly more likely to find a positive McConnell sign. In addition to the visual assessment of the RV function, the TAPSE value with a P <0.001 was the best quantifiable parameter for mapping the RV function in both groups, which is reflected in a higher correlation coefficient compared to S' (TAPSE, R=0.539, P<0.001; S', R=0.162, P<0.001). In addition to the visual assessment of the RV function, the TAPSE with a P <0.001 was the best quantifiable parameter for mapping the RV function in both groups. With the exception of S' in patients with a complicated clinical course, there were no significant differences in mTDI parameters.

4.2 Risk stratification

4.2.1 Comparsion between TnI, CK-MB and H-FABP

TnI is currently the established biomarker for laboratory risk stratification in PE (26). In order to review and compare how H-FABP, CK-MB and TnI indicate demographic, clinical and echocardiographic data of the deceased and / or patients with a complicated clinical course, the results after H-FABP, CK-MB and TnI were stratified. Overall, 26 out of 161 patients (16.1) had a positive H-FABP test result, 41 (25.5%) had positive CK-MB and 66 out of 161 (41%) had elevated TnI levels.

Demographic data

Table 4.9 compares the basic data of H-FABP, CK-MB and TnI-positive patients. Patients with positive laboratory parameters had significantly more acute onset of PE. Furthermore, it is noticeable that patients with positive biomarkers showed significantly more diabetic metabolic status. H-FABP- and CK-MB positive patients often had a positive history for typical DVT risk factors (P = 0.009). In patients with positive CK-MB levels creatinine and urea were significantly increased.

Table 4. 9 Basic data depending on H-FABP, TnI, CK-MB

	H-FABP			Troponine I			CK-MB		
	positive (n=26)	negative (n=135)	P	positive (n=66)	negative (n=95)	P	positive (n=41)	negative (n=120)	P
Age (years); mean±SD	67.7 ± 15.3	69.1 ± 13.1	0.627	68.7 ± 13.3	69 ± 13.7	0.698	68.7 ± 15.4	69.2 ± 12.8	0.830
Gender (females); N (%)	11 (42.3)	79 (58.5)	0.127	39 (59.1)	51 (53.7)	0.354	28 (68.3)	60 (50)	0.290
Acute onset (<3 days); N (%)	16 (61.5)	45 (33.3)	0.007	34 (51.5)	27 (28.4)	0.003	22 (53.7)	38 (31.7)	0.007
Typicale anamnese; N (%)	14 (53.8)	37 (27.4)	0.009	25 (37.9)	26 (27.4)	0.407	13 (31.7)	37 (30.8)	0.009
DVT; N (%)	17 (65.4)	96 (71.1)	0.559	47 (71.2)	66 (69.5)	0.982	28 (68.3)	83 (69.2)	0.844
Malignancy; N (%)	7 (26.9)	22 (16.3)	0.197	17 (25.8)	12 (12.6)	0.033	10 (2.4)	18 (15)	0.303
Hypertonus; N (%)	17 (65.4)	107 (79.3)	0.124	47 (71.2)	77 (81.1)	0.423	33 (80.5)	88 (73.3)	0.217
Diabetes; N (%)	13 (50.0)	33 (24.4)	0.008	25 (37.9)	21 (22.1)	0.029	19 (46.3)	25 (20.8)	0.008
Dyslipidemia; N (%)	13 (50.0)	66 (48.9)	0.917	39 (59.1)	40 (42.1)	0.034	19 (46.3)	59 (49.2)	0.330
Nicotine; N (%)	3 (11.5)	12 (8.9)	0.670	5 (7.6)	10 (10.5)	0.762	3 (7.3)	12 (10)	0.714
BMI (kg/m²); mean±SD	29.8 ± 6.9	29.1 ± 5.5	0.559	29.9 ± 6.9	28.7 ± 4.6	0.222	30.7 ± 6.6	28.7 ± 5.4	0.191
Creatinine (µmol/l); median (IQR)	127 (86-203)	98 (82-122)	0.026	99 (83-139)	102 (83-124)	0.126	148.3 (119-189)	109.1 (102-116)	<0.001
Urea (mmol/l); median (IQR)	7.9 (5.9-16.5)	6.8 (5.2-9.5)	0.254	6.9 (5.2-10.2)	6.8 (5.3-9.6)	0.856	10.6 (8.3-13.2)	7.9 (7.1-8.9)	0.003
GFR (ml/min); mean±SD	50 ± 14	58 ± 18	0.128	56 ± 22	57 ± 17	0.327	49 ± 20	58 ± 18	0.270

Clinical risk parameter

H-FABP, TnI and CK-MB positive patients have significantly lower blood pressures and higher heart rates compared to biomarker negative patients as depicted in Table 4.10.

Biomarker and endpoints

Table 4.11 shows the endpoints depending on the biomarker status. 15 patients of 26 H-FABP-positive died (57.7%). One deceased (0.7) was H-FABP-negative ($p < 0.001$). In contrast, 13 out of 66 (19.7%) TnI-positive patients died and 3 out of 95 (3.2%) TnI-negative patients ($P = 0.001$). From 41 CK-MB positive patients 14 (34%) died within 30 days vs. 1 patient who was CK-MB negative ($P < 0.001$).

The φ correlation coefficient for nominal scaled data was 0.701 for H-FABP, 0.513 for CK-MB and 0.272 for TnI, so a strong correlation between h-FABP and 30-day mortality can be assumed.

Looking at the surviving patients (Table 4.11, bottom panel), it is further noted that a positive H-FABP test was highly significant for complicated clinical course (7 out of 11 vs. 18 out of 134 patients, $P < 0.001$). A φ correlation coefficient of 0.352 confirms a weak to medium correlation for H-FABP and a complicated clinical course.

Table 4. 10 Clinical parameters depending on H-FABP, TnI and CK-MB

	H-FABP			Troponine I			CK-MB		
	positive (n=26)	negative (n=135)	P	positive (n=66)	negative (n=95)	P	positive (n=41)	negative (n=120)	P
RR_{sys} (mmHg); mean±SD	111 ± 19	136 ± 22	<0.001	126 ± 22	136 ± 24	0.018	119 ± 23	136 ± 24	<0.001
Heart rate (min^{-1}); mean±SD	108 ± 21	89 ± 18	<0.001	97 ± 19	88 ± 19	0.005	99 ± 22	89 ± 18	0.015
SaO_2 (%); mean±SD	91.6 ± 6.7	93.0 ± 5.0	0.443	92.9 ± 4.8	92.7 ± 5.4	0.843	92.7 ± 5.8	92.7 ± 4.9	0.978

Table 4. 11 Endpoints depending on H-FABP, TnI and CK-MB

Endpoint	H-FABP			Troponine I			CK-MB		
	positive (n=26)	negative (n=135)	P	positive (n=66)	negative (n=95)	P	positive (n=41)	negative (n=120)	P
30-day mortality; N (%)	15 (57.7)	1 (0.7)	<0.001	13 (19.7)	3 (3.2)	0.001	14 (34.1)	1 (0.8)	<0.001
	positive (n=11)	negative (n=134)	P	positive (n=53)	negative (n=92)	P	positive (n=39)	negative (n=114)	P
Complicated clinical course; N (%)	7 (63.6)	18 (13.4)	<0.001	10 (18.9)	15 (16.3)	0.553	3 (7.7)	21 (19.8)	0.082
- Resuscitation; N (%)	2 (18.1)	0 (0.0)	0.004	1 (1.9)	1 (1.1)	0.691	13 (33.3)	4 (3.8)	<0.001
- Lysis; N (%)	3 (27.3)	15 (11.2)	0.078	6 (11.3)	12 (13.0)	0.762	12 (30.8)	17(14.2)	0.029
- Catecholamines; N (%)	5 (45.5)	7 (5.2)	0.001	7 (13.2)	5 (5.4)	0.102	16 (41.0)	12 (10.5)	<0.001
- Embolectomy; N (%)	1 (9.1)	0 (0.0)	0.076	1 (1.9)	0 (0.0)	0.363	0 (0.0)	1(0.9)	0.557

4.2.2 Echocardiography

Table 4.12 stratifies the echocardiographic values for H-FABP, TnI and CK-MB status. Compared with Table 4.7, it becomes clear that the echo parameters of H-FABP and TnI-positive patients are essentially the same as those of deceased patient. Thus, the frequency of an enlarged RV, the RV / LV index, the frequency of the paradoxical septal movement or the TAPSE have similar values. Measurements of H-FABP-positive patients more accurately reflect deceased values, which is particularly evident in the parameters RV / LV-Index and TAPSE. The TAPSE in H-FABP positive patients at 13.7 ± 4.0 mm correspond almost exactly to the value of deceased patients. For TnI positives, the TAPSE were significantly lower ($P < 0.001$). In patients with positive CK-MB levels paradoxical septal movement, positive McConnell-sign, reduced RV function, LVEF and TAPSE were significantly different compared to CK-MB negative patients.

For the mTDI parameters, different results were found. S' was significantly decreased in H-FABP-positive patients compared with H-FABP-negative patients (see Table 4.8). In TnI and CK-MB positive patients E’ was significantly decreased compared to TnI and CK-MB negative patients.

Table 4. 12 Echocardiografic parameters in H-FABP, TnI and CK-MB positive patients

	H-FABP			Troponin I			CK-MB		
	positive (n=26)	negative (n=135)	P	positive (n=66)	negative (n=95)	P	positive (n=41)	negative (n=120)	P
Enlarged RV; N (%)	25 (96.2)	103 (76.3)	0.022	58 (87.9)	70 (73.7)	0.028	31(75.6)	91 (75)	1.000
RV-diameter (mm); mean±SD	39.8 ± 4.3	36.5 ± 6.2	0.012	37.6 ± 5.3	36.6 ± 6.5	0.357	36.3 ± 6.7	37.3 ± 5.6	0.650
LV-diameter (mm); mean±SD	39.9 ± 5.5	43.7 ± 7.0	0.009	41.9 ± 6.3	44.0 ± 7.3	0.07	42.03 ± 7.7	43.7 ± 6.6	0.272
LV/RV ratio; mean±SD	1.02 ± 0.24	1.25 ± 0.33	0.001	1.15 ± 0.36	1.25 ± 0.32	0.033	1.22 ± 0.4	1.21 ± 0.28	0.965
RV/LV ratio; mean±SD	1.02 ± 0.21	0.86 ± 0.22	0.001	0.93 ± 0.22	0.85 ± 0.22	0.04	0.90 ± 0.28	0.87 ± 0.19	0.317
Sphericity index; mean±SD	1.58 ± 0.49	1.76 ± 0.44	0.338	1.68 ± 0.43	1.76 ± 0.46	0.7	1.78 ± 0.36	1.67 ± 0.46	0.507
Eccentricity index; mean±SD	1.7 ± 0.04	1.66 ± 0.44	0.885	1.53 ± 0.49	1.70 ± 0.45	0.114	1.9 ± 0.13	1.6 ± 0.49	0.386
PSM; N (%)	15 (57.7)	50 (37.0)	0.034	35 (53.0)	30 (31.6)	0.008	23 (56.1)	39 (32.5)	0.014
Positive McConnell; N (%)	20 (76.9	66 (48.9)	0.009	44 (66.7)	42 (44.2)	0.005	25 (61)	51 (42.5)	0.02
RVSP (mm); mean±SD	55 ± 14	54 ± 16	0.835	54 ± 13	55 ± 18	0.603	53.7 ± 15.6	54.9 ± 16.2	0.937
Reduced RV function; N (%)	24 (92.3)	97 (71.9)		55 (83.3)	66 (69.5)		31 (78)	92 (76.7)	
- non	2 (7.7)	38 (28.1)		11 (16.7)	29 (30.5)		9 (21.9)	30 (25)	
- low-grade	2 (7.7)	38 (28.1)		11 (16.7)	29 (30.5)		5 (12.2)	30 (25)	
- moderate	14 (53.8)	49 (36.3)	<0.001	31 (47)	32 (33.7)	0.002	19 (46.3)	47 (39.2)	0.06
- high-grade	8 (30.8)	10 (7.4)		13 (19.7)	5 (5.3)		8 (19.5)	13 (10.8)	
Tricuspid regurgitation	23 (88.5)	134 (99.3)		65 (98.5)	95 (100)		38 (92.7)	110 (91.6)	
-TI I°	5 (19.2)	60 (44.4)		22 (33.3)	44 (46.3)		12 (29.3)	47 (39.2)	
-TI II°	17 (65.4)	60 (44.4)	0.035	38 (57.6)	41 (43.2)	0.239	22 (53.7)	52 (43.3)	0.196
-TI III°	1 (3.8)	14 (10.4)		5 (7.6)	10 (10.5)		4 (9.8)	11 (9.2)	
LVEF (%); mean±SD	53 ± 9	55 ± 10	0.359	54± 10	56 ± 10	0.022	52 ± 12	56 ± 9	0.045
TAPSE (mm); mean±SD	13.7 ± 4.0	19.1 ± 4.7	<0.001	16.5 ± 5.4	19.4 ± 4.3	<0.001	16.7 ± 5.0	18.7 ± 4.8	0.006
S' (cm/s); mean±SD	10.1 ± 4.4	12.3 ± 3.0	0.033	11.3 ± 3.7	12.5 ± 3.0	0.106	10.9 ± 4.1	12.3 ± 3.1	0.098
E' (cm/s); mean±SD	7.7 ± 3.7	9.2 ± 3.7	0.152	8.0 ± 3.3	9.8 ± 3.8	0.032	7.5 ± 3.6	9.4 ± 3.6	0.032
A' (cm/s); mean±SD	12.1 ± 5.2	13.7 ± 4.8	0.269	12.6 ± 5.0	14.2 ± 4.6	0.056	12.9 ± 5.3	13.7 ± 4.8	0.525

4.2.3 30-day mortality in relation to H-FABP, TnI and CK-MB

Of the 16 patients meeting the primary endpoint, 15 (93.75%) had elevated H-FABP levels on admission compared to 11 (7.6%) of 145 30-day survivors (P < 0.001). Accordingly, quantitative concentrations of TnI and CK-MB were significantly higher among patients who met the primary endpoint compared to survivors (P < 0.001). Categorizing for each of the biomarkers, 15 of 26 (57.7%) H-FABP positive patients compared to one H-FABP negative patient (0.7) met the primary endpoint (P <0.001). When stratified for TnI, 66 of 161 (41%) patients had TnI levels > 0.115 ng/mL and of these TnI-positive patients, 13 (19.7%) compared to 3 (3.2) TnI-negative patients died during 30-day follow up (P = 0.001). When considering CK-MB test results, 41 (25.5%) patients had elevated plasma levels and of these patients 15 (36.6%) vs. 1 of 120 (0.8%, P < 0.001) died (H-FABP positive vs TnI positive patients, P < 0.001; H-FABP positive vs CK-MB positive patients P = 0.130; CK-MB positive vs TnI positive patients P = 0.07). Kaplan-Meier analysis (Figure 4.2) demonstrates significantly lower survival rates for each of the biomarkers compared to patients who were negative for the specific marker (p < 0.001). However, observed survival rates were substantially lower in the presence of both positive H-FABP and CK-MB test results.

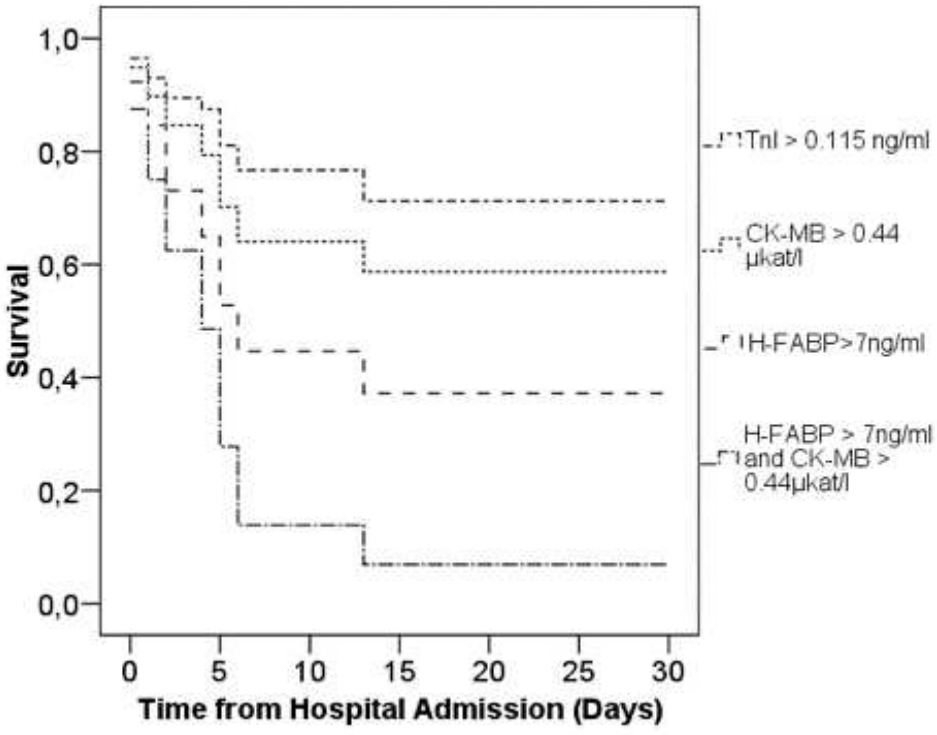

Figure 4. 2 Kaplan-Meier curves for the end point (30-day mortality) for TnI, CK-MB, H-FABP and combination of CK-MB and H-FABP

4.3 Receiver operating characteristics analysis and cut-off calculation

With regard to the endpoint, cut-off values for the clinical parameters systolic blood pressure and heart rate were estimated at 111 mmHg with an AUC of 0.895 (95% CI: 0.835 to 0.955, sensitivity 85%, specificity 83%, P<0.001) and 109 beats/min with an AUC of 0.805 (95% CI: 0.656 to 0.955, sensitivity 70%, specificity 80%, P=0.001). For TnI and CK-MB, calculated cut-off values were 0.115 ng/ml (AUC 0.713, 95% CI: 0.577 to 0.850, sensitivity 77%, specificity 69%, P=0.004) and 0.44 µkat/l (AUC 0.889, 95% CI: 0.793 to 0.986, sensitivity 82%, specificity 82%, P<0.001), respectively (Fig. 4.3, Table 4.13). The receiver operating characteristics analysis suggested that positive H-FABP test with AUC 0.928 (95% CI: 0.858 to 1.004, sensitivity > 90%, specificity > 90%, P<0.001) on admission is a powerful predictor of 30-day outcome in normotensive patients with PE (Fig. 4.3). The AUC of H-FABP levels >7ng/ml in combination with CK-MB levels > 0.44 µkat/l did not differ from that of sole H-FABP (AUC 0.931, 95% CI: 0.835 to 1.026), because specificity increased as sensitivity slightly decreased. The threshold values determined for the echocardiographic parameters RV / LV index and TAPSE were 0.99 and 15.5 mm, respectively, and the areas under the curves were 0.799 and 0.771 (P = 0.001; P < 0.001).

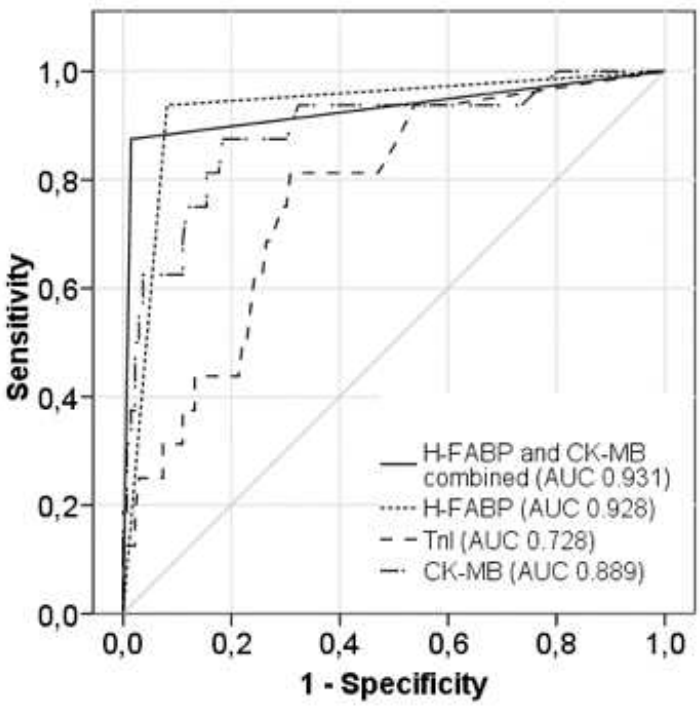

Figure 4. 3 The receiver-operating characteristic curve for H-FABP, CK-MB, TnI and combination of CK-MB and H-FABP on admission with regard to the 30-day mortality. AUC-comparison of laboratory parameters: H-FABP vs. TnI p=0.07; H-FABP vs. CK-MB p=0.08; CK-MB vs. TnI P=0.046.

Table 4. 13 Receiver-operating characteristics analysis and cut-off calculation selected quantitative parameters with regard to the 30-day mortality

		Cut-off	sensitivity	specificity	AUC	95% CI	P
RR_{sys}	mmHg	111	85.3	83.2	0.895	0.835 - 0.955	<0.001
HR	min^{-1}	109	69.7	79.8	0.805	0.656 - 0.955	0.001
TnI	ng/ml	0.115	77.2	68.8	0.713	0.577 - 0.850	0.001
CK-MB	µkat/l	0.44	82.4	81.7	0.889	0.793 - 0.986	<0.001
RV/LV		0.99	80.0	71.5	0.799	0.698 - 0.900	<0.001
TAPSE	mm	15.5	61.5	76.6	0.771	0.655 - 0.886	0.001

Table 4.14 shows the values for the complicated clinical course. Accordingly, cut-off values could not be determined for the laboratory values, since these are not significantly different. The TAPSE is most meaningful with an area under the curve of 0.831. A cut-off value of 17.5 mm was calculated with a sensitivity of 92.0% and a specificity of 68.4%.

Table 4. 14 Receiver-operating characteristics analysis and cut-off calculation selected quantitative parameters with regard to complicated clinical course

		Cut-off	sensitivity	specificity	AUC	95% CI	P
RR_{sys}	mmHg	120	43.5	87.5	0.683	0.552 - 0.808	<0.006
HR	min^{-1}	96	58.3	69.5	0.657	0.547 - 0.766	0.018
RV/LV		0.90	64.0	65.5	0.693	0.585 - 0.802	0.002
TAPSE	mm	17.5	92.0	68.3	0.831	0.760 - 0.902	<0.001
S’	cm/s	10.25	55.6	79.4	0.682	0.536- 0.828	0.019

4.4 Logistic regression analyses

4.4.1 Primary endpoint

In order to identify potential predictors for increased mortality from the examined variables, a logistic regression analysis was performed.

The univariate analysis showed that the following factors are associated with the primary endpoint of 30-day mortality:

- Hyperlipoproteinemia, cancer
- Lower systolic blood pressure, increase heart rate
- RV/LV index, paradoxical septal movement and TAPSE

Table 4. 15 Logistic regression analysis in relation to 30-day mortality

	univariate			***multivariate***		
	OR	(95% CI)	p-value	OR	(95% CI)	P-value
Diabetes	2.8	(0.9 - 8.0)	0.056	1.6	(0.5 - 5.2)	0.396
Hyperlipoproteinemia	0.3	(0.1 - 1.0)	0.038	0.7	(0.07 - 6.5)	0.754
Cancer	3.2	(1.1 - 9.6)	0.05	3.3	(0.9 - 11.3)	0.063
Systolic blood pressure	0.9	(0.8 - 0.9)	<0.001	0.8	(0.8 - 0.9)	<0.001
Heart rate	1.1	(1.0 - 1.1)	0.001	2.1	(0.7 - 13.6)	0.139
H-FABP (> 7 ng/ml)	182.7	(22.0 - 1515.5)	<0.001	27.1	(2.1 - 352.3)	0.001
Troponin I (>0.115 ng/ml)	7.5	(2.1 - 27.6)	0.001	2.4	(0.3 - 20.2)	0.422
CK (>2.85 µkat/l)	1.2	(1.1 - 1.4)	0.001	0.4	(0.05 - 3.2)	0.388
CK-MB (>0.44µkat/l)	4.0	(2.1 - 7.9)	<0.001	5.3	(1.3 - 23.3)	0.002
RV/LV ratio	6.2	(1.7 - 22.8)	0.002	4.8	(1.1 - 20.7)	0.056
PSM	6.9	(1.9 - 25.4)	0.001	2.8	(0.6 - 13.5)	0.187
McConnell sign	2.9	(0.9 - 9.3)	0.062	1.9	(0.1 - 4.4)	0.883
TAPSE	0.8	(0.7 - 0.9)	0.001	0.4	(0.1 - 1.6)	0.192

After adjustment, systolic blood pressure on admission, H-FABP, and CK-MB remain independent predictors of the primary endpoint in multivariate analysis. Patients with a positive H-FABP test have an approximately 27-fold increased mortality risk (OR 27.1; 95% CI 2.1 - 352.3) compared to patients with a negative test result. The presence of a higher blood pressure reduces the mortality risk by approximately 0.8-fold (OR 0.8, 95 CI 0.8 - 0.9), which in turn corresponds to a 1.2-fold higher risk at lower blood pressure levels. Increased CK-MB values increase the mortality risk 5-fold (OR 5.3, 95% CI 1.3 - 23.3).

4.4.1 Secondary endpoint

The univariate analysis showed that the following factors are associated with the secondary endpoint, complicated clinical course:

- H-FABP
- Lower systolic blood pressure, increase heart rate
- RV/LV index, McConnell sign, TAPSE and S’

After adjustment in the multivariate analysis, a positive H-FABP test with an approximately 5-fold increased risk (OR 4.8, 95% CI 1.1 - 21.1) remains as a predictor compared to H-FABP negatives for a complicated clinical course. At higher TAPSE values, the risk is reduced approximately 0.8-fold (OR 0.8 95% CI 0.7 - 0.8). Thus, a reduced TAPSE, increases the risk 1.3 times (OR 1, 3, 95% CI 1.2 - 1.5) for a complicated clinical course.

Table 4. 16 Logistic regression analysis in relation to complicated clinical course

	univariate			*multivariate*		
	OR	(95% CI)	p-value	OR	(95% CI)	P-value
Systolic blood pressure	0.9	(0.9 - 1.0)	0.004	0.4	(0.1 - 1.1)	0.07
Heart rate	1.1	(1.0 - 1.1)	0.021	1.9	(0.7 - 5.1)	0.2
H-FABP (> 7 ng/ml)	11.3	(3.0 - 42.4)	0.001	4.8	(1.1 - 21.1)	0.036
RV/LV ratio	4.3	(1.7 - 10.7)	0.002	1.8	(0.5 - 6.4)	0.345
McConnell sign	9.6	(2.7 - 33.8)	<0.001	1.3	(0.2 - 6.3)	0.756
TAPSE	0.7	(0.6 - 0.8)	<0.001	0.8	(0.7 - 0.8)	0.001
S‘	0.8	(0.7 - 0.9)	0.019	0.7	(0.2 - 2.5)	0.627

4.5 H-FABP in combination with other parameters

Based on the results from regression and ROC curve analysis, a combination of different markers to improve risk stratification seems to be possible and useful.

4.5.1 Primary endpoint

In order to test whether the prognostic value of H-FABP can be further improved with regard to the 30-day mortality, various parameters were combined with H-FABP. Table 4.17 shows the exact values that change by combining several parameters compared to H-FABP alone.

The Positive Predictive Value (PPV) indicates the likelihood of dying if the test result is positive (or if there is a combination of positive H-FABP and other positive test parameters). The Negative Predictive Value (NPV), on the other hand, represents the probability of survival if the test result is negative.

Table 4. 17 H-FABP in combination with laboratory or echo parameters based on the 30-day mortality

Combination	PPV %	NPV %	FP %	FN %	accuracy %	φ
H-FABP (alone)	57.7	99.3	42.3	0.7	92.5	0.701
H-FABP;RR_{sys}	66.7	97.2	33.3	2.8	93.8	0.673
H-FABP;TnI	61.9	97.9	38.1	2.1	93.4	0.673
H-FABP;CK-MB	87.5	98.6	12.5	1.4	97.5	0.861
H-FABP; RV/LV	72.2	97.9	27.7	2.1	95.0	0.739
H-FABP;TAPSE	60.0	95.3	40.0	4.7	93.0	0.490
H-FABP; PSM	75.0	97.2	25.0	2.8	95.0	0.722
H-FABP;PSM;RV/LV	80.0	97.3	20.0	2.7	95.7	0.751

From the calculated data, it can be seen that various combinations of H-FABP with systolic RR, laboratory or echo parameters provide improved levels of PPV than H-FABP alone. At once, the increase in PPV is accompanied by a decrease in the false-positive (FP) rate. Conversely, there is a decrease in NPV and an increase in false-negative (FN) results. Specifically, the combination of H-FABP with the CK-MB identified as an independent risk factor in the regression analysis provides the best results (Table 4.17):

- The PPV improves to 87.5% (decrease false positive to 12.5%) at only
- Slight decrease in NPV to 98.6% (increase from false-negative to 1.4%) with a
- Total accuracy, which is highest at 97.5%
- The φ correlation coefficient improves significantly with 0.861 and approaches a very high correlation with respect to the 30-day mortality.

The combination of H-FABP with TnI, on the other hand, only marginally improves stratification by tripling the false-negative rate and inferior correlation.

Improvements are also evident when the H-FABP test and echocardiographic markers of RVD are considered together. In particular, the combined detection of a positive H-FABP test with a simultaneously increased RV/LV index or the presence of a paradoxical septal movement or both gives better results than for H-FABP alone. However, these seem to be inferior to the combination H-FABP / CK-MB.

The combinations listed in Table 4.17 were again reviewed with multivariate logistic regression. The combination of H-FABP and CK-MB was chosen as the best of all variants (OR 163.4 95% CI 12.3 - 2164.4, $p < 0.001$). The combinations of H-FABP and systolic blood pressure (OR 9.4 95% CI 0.6 - 146.4, $p = 0.1$) and H-FABP and RV / LV-Index (OR 14.8 95% CI 1.0 - 227.7, $p = 0.06$) were selected in the model but were not significant.

In summary, it can be deduced that patients with a negative H-FABP test showed a greater than 99 probability of survival. Conversely, the probability of a fatal course with positive H-FABP and a CK-MB of> 0.44 µkat / l was 87.5%.

4.5.2 Secondary endpoint

For a complicated clinical course, the values for the two predictors H-FABP and TAPSE and their combination are shown in Table 4.18.

The combination of positive H-FABP test and reduced TAPSE achieves a PPV of 70.0%, but with an NPV of 86.7%, which corrrensponds to a false-negativ rate of 13.3% corresponds. The highest NPV was 97.5% for the TAPSE alone and φ correlation coefficient with a value of 0.440. A TAPSE > 17.5mm therefore exclude a complicated course with 97.5% probability.

The low-test accuracy of 70.3% results mainly from the low PPV of 35.9%. Other parameter combinations are significantly less the shown values.

Table 4. 18 H-FABP and TAPSE based on complicated course

Combination	PPV %	NPV %	FP %	FN %	accuracy %	φ
H-FABP (alone)	63.6	86.6	36.4	13.4	84.8	0.352
TAPSE (alone)	35.9	97.5	64.1	2.5	70.3	0.440
H-FABP;TAPSE	70.0	86.7	30.0	13.3	85.5	0.380

5 Discussion

PE with intermediate mortality risk occupies a distinct position within the spectrum of the disease. In contrast to the high-risk PE presenting with shock and severe right heart dysfunction, patients with intermediate mortality risk show stable hemodynamic conditions. However, they differ from the group of low-risk patients in the incidence of RVD, which may be manifested by an abnormal echocardiogram with specific changes or by the increase in cardiac biomarkers. Despite initially stable circulatory conditions, the mortality rate is at least 10 times higher than in low-risk patients, which questions previous management strategies (26). In particular, the question arises as to whether the therapy intensity of sole anticoagulation in intermediate risk is still adequate, or whether a subpopulation of patients with a significantly higher mortality risk exists within the intermediary risk group, which requires more intensive therapy. Konstantinides et al randomized 256 normotensive patients to either a heparin-plus-placebo or a heparin-plus-alteplase group (98). The heparin-plus-alteplase group demonstrated significantly better overall survival; conversely, heparin plus placebo therapy was associated with a 3-fold higher mortality or treatment escalation risk. Metaanalyses with patients not stratified for the risk of mortality did not show any benefit of routine thrombolysis in normotensive hemodynamic conditions (99, 100). In the Pulmonary Embolism Thrombolysis study (PEITHO), PE patients with intermediate mortality risk were randomized to either heparin alone or heparin plus tenecteplase. This important study showed that fibrinolytic therapy in patients with intermediate-risk PE prevents hemodynamic decompensation but increases the risk of major bleeding (54).

Prior to any necessary therapy adjustment, risk stratification of unselected patients with PE is of paramount importance and, alongside therapy, an important component of an adapted management strategy. Current models of hemodynamically stable PE patients rely on the detection or exclusion of RVD using imaging and laboratory cardiac markers. CT imaging and echocardiography are uncontroversial imaging methods (26). However, there is increasing evidence that the cardiac biomarkers TnT/I, which have been mainly used to date, may be inappropriate in patients with intermediate risk, as they do not have to be associated with an increased mortality risk in this patient population (11, 71).

H-FABP, a marker that has been used for some time in early diagnosis of acute myocardial infarction and correlates with a poor prognosis (8, 9, 62), was identified as a prognostic marker in both unselected patients with PE (63, 101) as well as in patients with intermediate-risk PE (11). The data in favor of H-FABP for risk stratification for this group of patients currently

comprises very few studies, some of which are based on the same study population, so that the studies presented in this study contribute to further scientific consideration. In addition to the right-heart-specific echocardiographic parameters such as TAPSE or mTDI investigated in this study, there are hardly any data available on the prognostic significance of these parameters for PE. Statements on the correlation of h-FABP with established and new echocardiographic markers of RVD are still missing.

In this study, H-FABP and TnI levels were analyzed in 161 consecutive patients with diagnosed PE and intermediate mortality risk, considering echocardiographic routine values and specific right ventricular parameters such as TAPSE and mTDI. The definition of the target criteria was based on 30-day mortality as primary endpoint and a complicated clinical course (defined as successful resuscitation, cardiogenic shock or hypotension, catecholamine therapy, escalation of therapy in form of thrombolysis, embolectomy, intubation and mechanical ventilation or extracorporeal membrane oxygenation) as a secondary endpoint.

The lethality within the first 30 days after hospital admission was 9.9%. A positive H-FABP test was independently associated with both increased 30-day lethality as well as complicated clinical course. Furthermore, CK-MB and systolic blood pressure were identified as independent predictors of lethal progression. Among the echocardiographic parameters, only the TAPSE was predictive of a complicated clinical course, whereas the mTDI values were found to be nonsignificant. Both H-FABP and TnI values correlated with echocardiographic parameters of RVD and patients with positive H-FABP test and abnormal echocardiogram had a significantly worse prognosis. However, the combination of H-FABP and CK-MB identified a subgroup of patients who had a particularly high mortality risk. TnI was not selected as an independent predictor in both endpoints.

5.1 Study population

The average age of 69 ± 13.5 years confirms that PE is a disease of the elderly over the age of 60 and highlights the importance of age as a major risk factor for PE (5, 102). In comparable study populations with normotensive PE patients, the average age was between 61 and 68 years (11, 88, 103). In more than 70% of patients a DVT could be detected on admission, which according to Sandler and Martin (104) can occur in up to 80 of cases and underlines the common etiopathogenesis of DVT and PE (22). However, only in 32% of patients, typical triggers for DVT were found. Thus, the remaining 68% insults are defined as idiopathic. The proportion of

idiopathic cases is therefore higher in this study population than the 25% to 50% described by White et al (105). However, this proportion refers exclusively to first manifestations, whereas in the study population no distinction was made between first or repeated episodes, which could explain the higher proportion.

The average increased BMI of 29 kg/m^2 in the study population underlines the importance of the risk factor obesity (20, 33). Mechanisms contributing to the increased risk of obesity include, in addition to mechanical compression and immobilization, increased synthesis of proinflammatory adipokines and prothrombotic and antifibrinolytic factors (106, 107). Increased BMI is further associated with more common occurrence of arterial hypertension, diabetes mellitus and hyperlipidemia associated with the metabolic syndrome (108).
Accordingly, arterial hypertension was found in 77%, hyperlipidemia in nearly 50%, and diabetes mellitus in nearly 30% of patients. Whether there is a joint risk profile for DVT and other cardiovascular diseases, such as coronary heart disease, is currently unclear. Holst et al. (2010) identified only obesity and nicotine use as joint risk factors in a Danish register of nearly 19,000 patients (109).

Although the medians of the renal parameters in the study population are close to the reference range, the average GFR was reduced at 56 ± 19 ml/min. Taking into account age-specific reference ranges according to the criteria of the Kidney Disease Outcome Quality Initiative (KDOQI), this may already indicate a beginning of a mild to moderate functional restriction (110). However, the one-time measurement is a snapshot of an acute situation depending on many factors. However, for the classification as chronic kidney disease (CKD), it would require further measurements over a period of 3 months (111), but this was not part of the study. Advanced reduction of GFR below 30 ml/min was defined as an exclusion criterion, as it may result in falsly elevated H-FABP and TnI values due to decreased renal elimination in severe renal impairment (112, 113).

5.2 Discussion of the main results (30-day mortality)

5.2.1 Mortality rate

The mortality rate of 9.9% found in the study within 30 days after hospital admission is in range of the data published on the group of normotensive patients with PE. Lethality up to 40 days after hospital admission is between 5% and 16% (63, 114, 115). In a meta-analysis with a total of 1366 normotensive PE patients, Jiménez et al. reported a mortality rate of 7.3% in the first 30 days after admission (71).

It was found that deceased patients tended to be younger and males, but the differences were not significant and thus were not conclusive. However, there are general indications that men may have a slightly higher risk of mortality compared to women, which among other things is explained by an increased risk of recurrent embolism (116).

In the case of deceased patients, there was a highly significant history of an acute onset within the last 3 days prior to admission. One possible reason may be a too rapid or insufficient adaptation to sudden pulmonary artery pressure increase. The possibility of adaptation depends, inter alia, on the thrombus load, the type and number of affected pulmonary vessels, and the fibrinolytic activity of the lung (23, 33, 117).

Malignant underlying diseases were found to be significantly more prevalent in the deceased and are named in the literature as a risk factor for a lethal course (118).

Significantly reduced GFR in deceased patients should be discussed from a variety of perspectives: On the one hand, the clinical and echocardiographic parameters (Tables 4.4 and 4.7) show that there was a high degree of paradoxical septal movement in this group on admission, leading pathophysiologically to the limitation of LV filling and function and thus to decreased blood pressure and increased heart rate values. Endogenous catecholamine release may already reduce renal blood flow and function. On the other hand, it is possible that a pre-existing renal dysfunction already existed and this alone or by way of an acute chronic renal failure could have contributed to a critical clinical course of PE. In this context, Falgá et al. reported an increased mortality risk in PE patients with impaired renal function (119). However, the authors compared patients that had a GFR below 30 ml/min with patients that had a GFR above 30 ml/min. It is likely that there is a general relationship between decreased GFR and lethality. It should also be considered that the average GFR was already decreased at hospital admission in the overall population (see 4.1).

5.2.2 H-FABP, CK-MB and systolic blood pressure predict an increased 30-day mortality

The logistic regression analysis examined almost all of the collected data, clinical, laboratory and echo parameters. In the univariate analysis for H-FABP a 183-times higher mortality risk was found. Compared to other studies, this value is distinctly higher, probably due to the high proportion of deceased patients among H-FABP-positive patients or due to the low total number of positive H-FABP tests. Dellas et al. and Lankeit et al. reported a 72-fold and 37-fold increased risk of complications and mortality associated with H-FABP positive patients in univariate logistic regression (11, 88). Similary, a positive H-FABP test increases the risk of

mortality in the present work by about 27-fold. This result is comparable to the data from Lankeit et al. (88) and Dellas et al. (11), which report a total of 37-fold and 26-fold increased risk. However, in both studies the results are based on quantitative H-FABP measurements. Furthermore, based on the regression analysis, it can be concluded that TnI is not an independent predictor of an increased 30-day mortality, as multivariate increased mortality risk could not be confirmed. The observations of other studies (63, 71, 88) can thus be confirmed. Furthermore, TnI is unlikely to be a biomarker for risk stratification of PE with intermediate risk with regard to a possible escalation of therapy. H-FABP is superior to TnI in direct comparison. The simultaneous measurement of both parameters reveals no further advantage; however, definitive statements can only be confirmed by a randomized study.

In the multivariate regression model, systolic blood pressure was also identified at admission as an independent predictor of increased 30-day mortality. The significance of blood pressure for risk stratification is also discussed in Section 5.2.4. However, the significance of systolic blood pressure as a predictor may only be due to the high prevalence of hypertensives (almost 80%) in the study population. On the other hand, the influence with a 1.2 times higher risk can be graded as low.. There is no information in the literature about the assessment of blood pressure for the further estimation of the mortality risk within the group of patients with intermediate risk PE. Dellas et al. proposed heart rate as a clinical parameter for further risk stratification in addition to H-FABP as they found an increase in the mortality and complication risk at values above 94 beats per minute (11). In the present study, a higher heart rate (threshold after ROC analysis 110 beats per minute) was associated with a 1.1-fold (95% CI 1.0 - 1.1) higher mortality risk. However, this was not an independent predictor after multivariate analysis.

In the multivariate model, the CK-MB was still selected as a highly significant value for the prediction of increased mortality. Although Adams et al. (120) mentioned increased CK-MB activity in PE more than 20 years ago, there are only sparse data available for use as prognostic markers until then: Gallotta et al. described the CK-MB for the first time as a TnI-independent predictor of increased hospital mortality in normotensive patients with PE (121). Stein et al. found a 7-fold increase in mortality risk in a study of 392 patients with stable circulation in LAE, but with limited predictive value due to the low prevalence of CK-MB displacement (7.4% of all patients) (12). In the present study, there was an increase in CK-MB activity in 41 (25.5%) patients which was independently associated with a 5-fold higher mortality risk. It should be noted that Stein et al. (120) used the CK-MB mass for evaluation, while CK-MB activity was determined for the present study. The extent to which CK-MB mass

and activity are comparable can not be assessed based on the scarcely available data on the PE. The ROC analyses confirmed the results of the regression analysis, with the AUC of CK-MB being significantly greater than that of TnI (Figure 4.3). Statistically, CK-MB selection suggests a higher relative frequency of fatal outcome with increased CK-MB (14 of 41, 34%) compared to elevated TnI (13 of 66, 19.7%). Reasons for the differential excursion of TnI and CK-MB (and ultimately also H-FABP) might be due to the different release kinetics, so that laboratory results are contingent on the time of measurement. The occurrence in the serum depends on appropriate damage of further parameters such as molecular size and intracellular localization: The CK-MB (86kDa), like H-FABP, is almost completely cytosolic, while TnI (23kDa) is more than 90% bound to myo-filaments as a structural protein. Despite its smaller molecular size, the release of TnI is delayed compared to CK-MB and occurs over a longer period (extended diagnostic window). At the molecular level, the release of TnI and CK-MB continues to be influenced by intracellular messengers such as calcium. The intracellular messenger substances are dependent on the cell's response to ischemic damage (oncosis, apoptosis or necrosis) and thus cause possibly differently timed releases of proteins such as TnI and CK-MB (122). In addition, there are indications that CK-MB and troponin may be distributed differently between LV and RV, so that correspondingly different marker constellations could occur in serum in ischemia, depending on the localization (123, 124). Bozbay et al. could shown in PE patients treated with thrombolytic tissue-plasminogen activator that increased CK-MB levels had a higher incidence of in-hospital mortality (77). However, at the present time, there are no further studies on the role of CK-MB in intermediate risk PE patients in the literature, so that the present work provides important findings that can contribute to risk stratification in intermediate risk patient. Whether it is more useful to determine the CK-MB mass or its activity should be investigated in further studies.

There were no echocardiographic parameters among the values suitable for predicting an increased 30-day mortality. Kucher et al. (58) reported a 2-fold increased mortality risk in the presence of RVD in the echocardiogram after evaluating data sets of 1035 normotensive patients in the ICOPE registry. In the univariate analysis, an almost 7-fold increased risk in case of right ventricular dilatation or paradoxical septal movement was found, however, that could not be confirmed in the multivariate regression analysis. A similar result was also reported in a meta-analysis by Coutance et al. who investigated a total of 8 studies with a total of 1,249 patients and found a slight association between RVD and mortality, but without being able to derive prognostic predictions for the clinical routine (59). Dellas et al. (2010) also found no

association between echocardiographically diagnosed RVD and 30-day mortality for the group of PE patients with intermediate mortality risk (11).

5.2.3 The combination of H-FABP with other parameters improves risk stratification

Among the combinations of the different measured parameter compared in Section 4.5, the variant H-FABP/CK-MB appears of particular importance. Simultaneously increased plasma levels of both biomarkers appear to be specific in patients with a high mortality risk according to the results of this work. This association was presented for the first time in this study. Favorable combinations of H-FABP with echocardiographic parameters for risk stratification can also be confirmed by other authors (12, 88), but in this study, those were inferior to the combination H-FABP/CK-MB. As in other studies, a negative H-FABP test excludes more than 99 of lethal outcomes (11, 88). For this form of risk stratification, no echocardiogram would be required initially. Nevertheless, an echocardiogram should always be performed to rule out further factors influencing the prognosis, such as RV thrombi or differential diagnoses (26).

Furthermore, a complicated clinical course could be excluded in patients with TAPSE values above 17.5 mm with 97.5 probability. Conversely, a decreased TAPSE in combination with a positive H-FABP test result can provide increased vigilance for the detection of incipient complications. Practical consequences could be, for example, early admission to intensive care with close (invasive) circulatory, blood gas, and biomarker monitoring. More invasive treatment options required would then be possible without much delay, which may also improve the prognosis. Other collected parameters do not appear sufficiently indicative for complicated clinical course.

Based on the identified prognostic parameters and the mentioned parameter combinations, the development of a separately validated score, from which the further diagnostic and therapeutic management strategy results, seems possible and meaningful.

5.2.4 Risk profile of deceased patients

In comparison, lower blood pressure values at higher heart rates are to be regarded as signs of marked haemodynamic impairment in patients that later deceased, considering the echocardiographic findings. Similar data can be found in Gallotta et al. (121), Dellas et al. (11) and Kostrubiec et al. (103), however, blood pressure differences between deceased and survivors are less pronounced than in the present work. In the current ESC guidelines, a pulse rate $\geq$ 110/min and a systolic blood pressure $\leq$ 100mmHg are positive values for the pulmonary embolism severity index for risk stratification. In the present study, a 1.2-fold increase in the

risk of mortality (see regression analysis in Table 4.15 was found at a threshold of 111 mmHg (see ROC analysis, Table 4.13). The value could serve as a threshold for further stratification within the group of intermediate risk PE patients. There are currently no data in the literature for this. On the other hand, it is possible that the high proportion of patients with arterial hypertension (77% in the study population) might have classified patients as high-risk patients, which would have excluded them from the study.

As expected, the medians of all myocardial ischemic markers were significantly increased in patients who died later compared to survivors (Table 4.5), so that significant myocardial damage in this group must generally be assumed. Their increase can be explained pathophysiologically (see 1.1.5) by ischemia or microinfarction of the RV (98, 101). Prognostic implications are particularly discussed in the preceding sections 5.2.2 and 5.2.3. There was no significant difference between groups for D-dimers, although differences and even prognostically relevant statements have been reported in the literature (125).

The echocardiographic data for the 30-day mortality (Table 4.7) show that, according to the criteria defined under 2.3.1, 80% (128 out of 161) of all patients had an abnormal echocardiogram on admission. Kreit et al. (44) showed that in at least 25% of all PE echocardiographic signs of an RVD can be identified. However, there is currently no standard definition on the echocardiographic criteria of RVD (26), so that data reported in the literature are always dependent on the criteria of the respective authors and therefore comparisons of prevalence are complicated. In line with the current ESC guidelines, only a complete normal right-heart echocardiogram has been described as non-dysfunctional (26), which puts into perspective the high prevalence of 80% in the study population. Comparable studies report prevalence rates between 33% and 72% (11, 88, 103, 126), whereby deviations among others result from different echo criteria. In the echocardiogram at admission an RVD could be confirmed for all patients that later deceased. The pathophysiological significance of restricted RV and LV function is reflected in the significantly increased or decreased values for RV and LV diameters and the size indices. Similary, paradoxical septal movement was found in more than 80% of deceased patients. Interestingly, the RVSP did not differ between the deceased and the survivors, although the visual assessment of the RVEF and the objectively measurable TAPSE of the deceased were significantly more decreased. The TAPSE values associated with the visual RVEF assement (Section 4.1.3), in turn, correlate well with more accurate MRI-based methods for RVEF determination (89). Reduced TAPSE values have been reported to a similar extent in patients with PE (127, 128), but data validated in large patient populations are lacking. In the present study, the mTDI parameters were equally limited in both the deceased and the

survivors, in which S' also correlated with the RVEF (Section 4.1.3). However, there were no significant differences in the endpoints. The measured values correspond to the values given in the literature: For the parameter S' values of 9.9 to 13.1 cm/s are found for patients with PE and RVD (128-130). Tueller et al. showed that threshold values for S' of 12 cm/s and 9 cm/s correlated with moderately or severely restricted RVEF (131). However, Rodriguez et al. found no correlation between S' and the severity of vascular pulmonary obstruction in PE (130). In the present work TAPSE performs significantly better than S' on RVEF (Section 4.1.3). Furthermore, mTDI parameters were considered in a larger study population for the first time under the criteria "30-day mortality" and "complicated clinical course". In view of nonsignificant differences for S', E' and A' between deceased and survivors of the study population, it can be assumed that no prognostically relevant statements can be derived from the examination of mTDI parameters in contrast to TAPSE. Several factors could contribute to this result: These include, for example, the RVSP distributed almost equally between deceased and survivors. Furthermore, it can not be ruled out that in addition to poor sound conditions, different examiners could be a source of measurement inaccuracies. Although the practical implementation of the study protocol provided for the echocardiographic examination to be carried out by the same, experienced examiner, it was not always possible to carry out this requirement in everyday hospital work. Thus, it is conceivable that possibly lacking routine in other examiners could have contributed to measurement inaccuracies, since the determination of right ventricular tissue Doppler parameters in contrast to the left ventricular measurement is currently not standard.

5.2.6 Risik stratification

Stratification of the basic data of the study population according to H-FABP, TnI, CK-MB (Table 4.9) results, with a few exceptions, in a similar distribution as in the case of deceased patients (Table 4.2). Noticeable among CK-MB, H-FABP and TnI-positive patients is the higher proportion of patients with diabetes mellitus, which may be an expression of increased cardiovascular risk in connection with arterial hypertension and increased BMI. Elevated H-FABP and TnI plasma levels have been described in patients with metabolic syndrome or isolated diabetes mellitus, and some authors have already considered arteriosclerosis markers in asymptomatic patients (132). To what extent a pre-existing arteriosclerosis favors RV infarction under acute dilatation as in PE, is still unclear. However, due to the pathophysiology of coronary heart disease, it is reasonable that myocardial ischemia may be more likely to develop in pre-existing strictures with RV dilatation. On the other hand, higher CK-MB/H-

FABP / TnI values in diabetics may be an expression of silent PE-independent myocardial ischemia. However, there was no significant difference between diabetics and non-diabetics in terms of endpoints. GFR slightly limited overall, there are no differences between biomarker-positive and -negative patients, so that false-positive laboratory values due to impaired renal function are unlikely.

CK-MB, H-FABP and TnI-positive patients had significantly lower blood pressure values and higher heart rates compared to the patients who died, although the differences were much more pronounced for H-FABP. Dellas et al. (11) also observed higher heart rates (100 vs. 90 beats per minute) in patients with H-FABP ≥ 6 ng / ml, but with no significant difference. Comparable data on systolic blood pressure as a circulatory parameter depending on H-FABP do not exist due to the limited studies so far.

The mortality rate among H-FABP-positive patients appears to be increased by 57.7% (15 out of 26). Puls et al. (133) investigated PE in a group of patients not differentiated according to the mortality risk (n = 107) and found complication and mortality rates of 41 (12 of 29) and 34% (10 of 29), respectively. Dellas et al. (11) investigated 126 patients with intermediate mortality risk and found complication and mortality rates of 28% (8 out of 29) and 14% (4 out of 29), respectively, among H-FABP-positive patients. However, the studies are only partially comparable for various reasons: Puls et al. (133) and Dellas et al. (11) belong to the same research group, which largely recruited their study populations from a common patient population (n = 73). The authors grouped the target criteria "death" and "complicated clinical course" into a common endpoint while they are considered separately in this study. In this context, Dellas et al. (11) discussed their findings on a low number of endpoints in their study. The study by Puls et al. also included patients with high-risk PE who were excluded in this study (133). Noticeable in this study, the proportion of H-FABP positive patients with 16.1% was low, while Dellas et al. (11) reported 23% of patients as H-FAB positive. However, Vuilleumier et al. (101) found a proportion of 18.1% H-FABP positive patients in the group with intermediate mortality risk in a comparative study of several biomarkers for longer-term risk stratification. Reasons for the comparatively high mortality rate can thus be seen both in the low total proportion of H-FABP-positive patients and in the use of a qualitative test. The rapid test, originally developed for the early diagnosis of heart attack, has a limit of 7 ng/ml (134). In PE, however, several authors have described and used limits of 6 ng/ml (11, 85, 133). This could be another possible explanation for different positive H-FABP values.

Stratification after TnI also results in a significant difference for the 30-day mortality with a mortality rate of 19.7% for those with positive TnI vs. 3.2% for those with negative TnI (P =

0.001). This has been described for unclassified PE (42, 135) and intermediate risk PE (121, 136). Compared to H-FABP, however, the difference is less pronounced, and the proportion of false-positive test results is significantly higher. Finally, TnI was not directly selected as an independent predictor in multivariate regression analysis.

It is well known that patients with PE have elevated CK-MB levels (120). However, very little is known about the prognostic value of CK-MB in PE patients. Gallotta et al. (121) described for the first time CK-MB as an independent predictor of increased hospital mortality in normotensive patients with PE regardless of TnI levels. Stein et al. (12) could show in a retrospective analysis that normotensive patients with high CK-MB mass levels upon admission had a 7-fold increased risk of death from PE, even though its prevalence was low. In our study CK-MB was another predictor of mortality and superior to TnI and right ventricular dilatation on echocardiography. Bozbay et al. could shown that increased CK-MB levels in PE patients treated with thrombolytic tissue-plasminogen activator were associated with higher incidence of in-hospital mortality (77). In our study we could show in normotensive PE patients that elevated CK-MB levels above a cut-off value of 0.44 µkat/L derived from ROC curve analysis are independently associated with a 5-fold increased risk of death. More importantly, when considered in combination, 16 patients were positive for CK-MB and H-FABP and 14 (87.5%) of these patients died within 30 days.

5.3 Discussion of further results (complicated clinical course)

5.3.1 Complication rate

The adjusted complication rate was 17.2% (25 of 145 patients). Deceased persons were not included in order to enable a separate evaluation of the two outcomes. The complication rate was described with 7% by Dellas et al. (11) for comparison, whereby the lethal courses were combined with complicated courses to a common end point. Basic demographic data for patients with a complicated history differed from patients with uncomplicated history except for the distribution of malignancies. The distribution of malignancy in favor of patients with an uncomplicated course can be difficult to justify in light of malignancy being a proven risk factor for complicated or lethal PE events (118). It would have been expected at least an even distribution or higher rates in patients with complicated course and those that are deceased. Patients may have had various stages of malignant disease, so that, for example, in the deceased rather an active disease was present. Upon admission to the database, no distinction was made between active and past, treated malignant disease, as VTE may also indicate the first onset or recurrence of a cancer (137). On the other hand, a random statistical effect in the sense of a

second type error or β-error is conceivable, the possibility of a protective effect of a malignant disease seems very unlikely and can be scientifically difficult to justify.

5.3.2 H-FABP and TAPSE predict a complicated clinical course course

According to the result of the multivariate regression analysis, a positive H-FABP test increases the risk for a complicated course by about 5-fold and a reduced TAPSE about 1.3-fold. For the use of TAPSE as a well quantifiable prognostic parameter in PE, there is currently little information in the literature. The few data available focus predominantly on mortality as an endpoint: Pruszczyk et al. (138) showed in a comparative study of several echocardiographic parameters (without mTDI and no simultaneous comparison of laboratory parameters) that normotensive patients with PE with lowered TAPSE values have an approximately 1.6-fold increased risk of mortality and complications. Another comparable study by Forfia et al. (139) identified TAPSE as a prognostic marker in patients with pulmonary hypertension, with a TAPSE less than 18 mm representing a 6-fold increased mortality risk. Furthermore, the mortality risk increased by 17% per mm of reduced TAPSE. It is questionable whether the data can be transferred to the clinical picture of acute PE, since the underlying pathophysiology and temporal dynamics are different.

5.3.3 H-FABP is more specific for lethal course

Compared with a lethal and complicated course, it is noticeable that in case of a positive H-FABP test the risk of a lethal course (OR 27.1, 95% CI 2.1 - 352.3) is more than 5 times higher, as for a complicated clinical course (OR 4.8, 95% CI 1.1 - 21.1). While 93% (15 out of 16 patients) had positive H-FABP test in the case of lethal course, only 28% of patients were H-FABP positive in complicated cases (7 out of 25 patients). The association of H-FABP and lethal course with $\varphi = 0.701$ was twice as high as that of H-FABP and complicated course ($\varphi = 0.352$). H-FABP thus appears to be more specific for a more pronounced RVD and to be better in predicting a potentially lethal course. So far, there are no comparable data in the literature.

5.3.4 Risk profile with complicated clinical course

Patients with a complicated course showed significantly lower blood pressure values and higher heart rates, similar to the deceased patients, compared to patients without therapy escalation, which also suggests impaired hemodynamics considering the echocardiographic data in this group (see Table 4.8). Oxygen saturation was also significantly reduced. This circumstance is difficult to assess as many patients initially receive oxygen from the ambulance or immediately

after arriving at the hospital. Hypoxemia and gas exchange disorders are less of a pathophysiological role in PE as patients are often well-oxygenated (5, 23).

In the laboratory parameters, only the H-FABP rapid test was found to be significantly more positive (see also 5.2.6), which could possibly be an expression of a mild transient right ventricular myocardial ischemia in right ventricular dilatation. Because of the smaller molecular size and localization of H-FABP in the cytoplasm, rapid plasma enhancement is possible even under transient ischemia, whereas release of structural proteins such as TnI requires longer ischemia times.

Echocardiographically, the ventricular size ratios (RV/LV index) were substantially similar to those in deceased patients, although less pronounced. Although there was also hemodynamic impairment in patients with a complicated course, a paradoxical septal movement could not be detected more frequently in this group. However, noticeable is the highly significant occurrence of the McConnell sign, a regional RV dyskinesia of the middle part of the free RV wall, with preserved contractility of the RV tip (90), compared to unimpaired patients. Surprisingly, TAPSE was found to be approximately the same in patients with a complicated clinical course as in those that have deceased, making it very well suited to indicate a significant systolic RV function restriction. However, deceased patients did not have significantly lower TAPSE scores than patients with complicated outcomes. Thus, the TAPSE is not likely to predict an increased risk of fatal outcome. The significant difference for S' also indicates the more limited RV function in patients with a complicated course. This is surprising in that, contrary to expectations, there was no significant difference between the deceased and the survivors for S'. However, this may result from the fact that in the group of surviving patients, the 25 patients with complicated course are included, so that overall no significant difference arises.

5.4 Qualtity criteria and threshold values for collected parameters

Quality criteria and thresholds for 30-day mortality were calculated for selected parameters (Table 4.13). The 111mmHg threshold found in the systolic blood pressure study population has not yet been validated against literature references for the group of intermediate risk PE. For the heart rate (threshold 110 beats per minute), Dellas et al. (11) used a threshold of 94 beats per minute for an equal AUC of 0.74, but the heart rate is not selected as an independent predictor. In the present study, the systolic blood pressure has a greater AUC with respect to the 30-day mortality with better sensitivity and specificity than the heart rate. Thresholds for TnI can only be compared to a limited extent between different studies because different

assayspecific reference ranges may exist depending on the laboratory test used. However, comparability is possible with the help of the AUC, which is slightly higher in TnI of 0.756 in this study compared to 0.67 in Dellas et al. In a direct comparison of the ROC curves, the AUCs of H-FABP and CK-MB were significantly larger than the AUC of TnI.

Among the echocardiographic parameters, the threshold of 1.0 prescribed for the RV / LV index (140) can be consistently confirmed. With respect to TAPSE, Pruszczyk et al. (138) reported thresholds of 15mm (present work 15.5mm in Table 3.13) for a potentially lethal course and of 20mm for a low-complication course. In patients with pulmonary hypertension Forfia et al. (139) reported a improved survival at values over 18mm. Based on this, a complicated course with a TAPSE value above 17.5 mm was unlikely in the present work (Table 4.14).

5.5 Limitations

There are several limitations in this study. First, although prospective, it was an observational and monocentric study.

Another problem is the heterogeneity within the study population regarding the time of conception and the duration of the symptoms which may have had effects on the plasma levels of the biomarkers. Formation of subgroups by symptom duration to produce homogeneity within the group of normotensive patients with PE has not yet occurred in any study. However, this could be useful against the background of different release kinetics.

The H-FABP test used is a commercially available dichotomous qualitative ELISA bedside test. The test is indicating only positive (H-FABP concentration <7 ng/mL) or negative (concentration >7 ng/mL) results. The test uses whole blood and shows results within 15 minutes. When H-FABP concentrations are close to the threshold value the interpretation of the test result can be difficult, especially in the presence of impaired renal function (113). Additionally, there is evidence that the cut-off might be lower than 7 ng/mL which might partly explain the lower incidence of positive H-FABP tests in this study (11, 133). Another limitation is the small sample size and that the study was focused only on the 30-day time period after hospital admission and did not perform long-term follow-ups. However, there is indication that H-FABP could be capable of assessing long term prognosis after intermediate risk PE (11, 88, 133). Another limitation is that we did not examine CK-MB mass levels. It is unclear whether CK-MB mass levels or activities are equally suitable for risk stratification. No account for

macro CK forms was done. With determination of CK-MB activity, interference with macro CK forms could be an issue leading to false positive test results.

Finally, no assessment of right-ventricular free wall strain was done because when the study was conducted a speckle-tracking echocardiography and strain trained physician was not general available in general. Several studies showed that right ventricular wall strain assessment is affected by the presence of acute PE, however they are non-specific and may be not pathological in haemodynamically stable patients, despite the presence of acute PE (141, 142). There are also data available that RV strain parameters were not correlated with hospital or long-term mortality (143). However, a recent study showed in patients with acute non-massive PE that RV free wall strain assessed with speckle-tracking was an independent prognostic marker for in-hospital events (144). Additional prospective randomized controlled trials will be necessary to identify which specific echocardiographic parameters are the most useful in risk assessment in acute PE and determine whether such information is of utility in identifying patients who could benefit from an intervention.

6 Conclusion

Normotensive patients with PE have a 30-day mortality risk of 10%. At hospital admission, lower systolic blood pressure values, H-FABP values more than 7 ng/ml and CK-MB values higher than 0.44 µkat/l predict a higher mortality. In particular, the combination of H-FABP and CK-MB can identify a potentially lethal subgroup. A relationship between elevated TnI levels and mortality risk can not be demonstrated by simultaneous measurement of H-FABP. The benefit of TnI for risk stratification in this patient group is inferior to that of H-FABP and CK-MB. The prompt echocardiographic examination is necessary in addition to the exclusion of differential diagnoses to gain mainly negative-predictive prognostic information, especially from RV/LV index and TAPSE. The combination of H-FABP and echocardiographic parameters for risk stratification may be taken into account, but it is lower in priority than the combination H-FABP/CK-MB.

MTDI does not provide additive prognostic information by itself or in combination with other values and is inferior to the measurement of TAPSE. The use of mTDI for risk stratification of normotensive patients with PE can not be substantiated on the basis of the available data.

In risk stratification, the study of H-FABP and CK-MB, as described in the present work, can be used and may replace TnI as an established marker. The individual test results, and in particular the combination of positive H-FABP test and increased CK-MB, could be included in the PE management algorithm, especially when addressing the issue of thrombolysis which routinely not recommended in this group of patients. The information obtained in this way could then be taken into account, for example, in an individual risk score that is yet to be developed and separately validated. However, prior prospective validation of these requires randomized, controlled trials.

7 Summary

The treatment of acute pulmonary artery embolism remains a challenge for modern medicine. While the risk-adapted treatment strategies for the groups with high and low mortality risk are essentially uncontroversial, uncertainty remains in patients with intermediate risk PE about the appropriate risk stratification and management. Despite therapy, the mortality rate of this form of pulmonary embolism is about 5-16%. It is possible that current concepts for risk stratification, based on the use and combination of troponin I (TnI) with imaging techniques such as echocardiography, only transfer to this patient group in limited capacity. Therefore, clinical research is increasingly focusing on other cardiac-specific biomarkers, such as cardiac muscle-specific fatty acid binding protein (H-FABP), which is already being used successfully in early-stage cardiac infarction diagnostics.

Aim of the study

The present study investigates the prognostic value of new myocardial laboratory markers as well as specific right ventricular echo parameters and contributes to risk stratification in PE with intermediate mortality risk.

Material and Methods

Between 2005 and 2010, 161 patients with proven PE and an initial systolic blood pressure above 90 mmHg were enrolled. All patients underwent TnI, creatine kinase isoenzyme MB (CK-MB), CK and D-dimers determination at the routine cardiology laboratory. All patients continued to receive a commercially available qualitative H-FABP rapid test (threshold 7 ng/ml). The routine echocardiographic examination with measurement of ventricular size ratios (RV/LV index), the mTDI parameters, the TAPSE and other standard parameters took place on the admission day. An intermediate mortality risk was based on the guidelines for echocardiographic signs of right ventricular dysfunction (RVD) or elevated cardiac muscle specific laboratory parameters. The primary endpoint was the 30-day mortality due to PE. The secondary endpoint was the occurrence of a complicated clinical course, defined by therapy escalation in the form of catecholamine administration, thrombolysis or embolectomy or resuscitation.

Results

In total, 16 out of 161 (9.9%) patients died within 30 days after hospital admission. The deceased had significantly higher plasma levels of TnI, and CK-MB compared to survivors. A

positive H-FABP test was found in 26 patients, of whom 15 (57.7%) died. In contrast, one of 135 H-FABP-negative patients died (0.7%, H-FABP positive vs. negative P <0.001). Stratification according to TnI resulted in a mortality rate of 19.7% (13 out of 66) among TnI-positive patients and 3.2% among those that were TnI-negative (3 out of 95, P = 0.001). In echocardiography, H-FABP positives exhibited significantly greater RV/LV indices (1.02 ± 0.21 vs. 0.86 ± 0.22, P = 0.001) compared to H-FABP negatives, and a significantly lower TAPSE (13.7 ± 4.0 mm vs. 19.1 ± 4.7 mm, P <0.001). There were no significant differences for the mTDI parameters. Multivariate logistic regression analysis identified H-FABP (OR 27.1 95% CI 2.1 - 352.3), CK-MB (OR 5.3 95% CI 1.3 - 23.3) and the systolic blood pressure on admisson (OR 1.2 95% CI 1.1 - 1.3) as independent predictors of 30-day mortality. The combination of positive H-FABP test and increased CK-MB resulted in a particularly high mortality risk: 14 of 16 patients with this laboratory constellation (87.5%) died. Conversely, the survival probability of H-FABP-negative patients was over 99%.

There was an increased risk of a complicated clinical course with a positive H-FABP test (OR 4.8 95% CI 1.1 - 21.1) and reduced TAPSE (OR 1.3 95% CI 1.2 - 1.5). TAPSE values above 17.5mm made a complicated course unlikely in 98% of the cases.

Conclusion

Our data support the hypothesis that H-FABP could be a promising prognostic marker in intermediate risk PE being highly associated with an unfavorable short-term outcome. Its clinical value in risk stratification seems to be superior to that of cardiac troponins. The combination of elevated H-FABP and CK-MB plasma levels indicates a particularly high risk of mortality. The clinical value of CK-MB in risk stratification of PE is unclear and might be underestimated and further studies are required. Increased H-FABP values correlate with echocardiographic markers of RVD. MTDI is not suitable for risk stratification in this patient group. Additional studies are necessary to identify which specific echocardiographic parameters are the most useful in risk assessment in acute PE with intermediate risk mortality.

Sažetak

Liječenje akutne embolije plućne arterije i dalje ostaje izazov za suvremenu medicinu. Iako su strategije liječenja prilagođene riziku za skupine s visokim i niskim rizikom od smrtnosti u osnovi nesporne, kod bolesnika sa srednjim rizikom za plućnu emboliju ostaje neizvjesnost o odgovarajućoj stratifikaciji rizika i zbrinjavanja pacijenta. Unatoč terapiji, stopa smrtnosti od ovog oblika plućne embolije je oko 5-16%. Moguće je da se trenutni koncepti za stratifikaciju rizika, temeljeni na upotrebi i kombinaciji troponina I (TnI) s tehnikama slikovnog prikaza, poput ehokardiografije, prenose na ovu grupu bolesnika u ograničenom kapacitetu. Stoga se klinička istraživanja sve više fokusiraju na druge specifične srčane biomarkere, poput srčano-mišićnog proteina koji veže masne kiseline (H-FABP), koji se već uspješno koristi u ranoj fazi dijagnostičkog postupka srčanog infarkta.

Cilj studije

Ova studija istražuje prognostičku vrijednost novih laboratorijskih markera miokarda, kao i specifične parametre ultrazvuka desnog ventrikula te doprinosi stratifikaciji rizika u pacijenata s plućnom embolijom sa srednjim rizikom smrtnosti.

Materijali i metode

Između 2005. i 2010. godine u istraživanje je uključeno 161 pacijenta s dokazanom plućnom ebmolijom i početnim sistoličkim krvnim tlakom većim od 90 mmHg. Za sve pacijente provedeno je mjerenje TnI, kreatin kinaze MB (CK-MB), CK i D-dimera u laboratoriju za rutinsku kardiologiju. Kod svih bolesnika učinjen je komercijalno dostupan kvalitativni brzi test H-FABP (prag osjetljivosti od 7 ng/ml). Rutinski ultrazvučni pregled s mjerenjem omjera veličine ventrikula (RV/LV indeks), mTDI parametrima, TAPSE i drugim standardnim parametrima obavljen je na dan prijema. Definicija srednje razine rizika od smrtnog ishoda zasnovana je na smjernicama za ultrazvučne znakove disfunkcije desne klijetke (RVD) ili na povišenim vrijednostima specifičnih laboratorijskih parametara za srčani mišić. Primarni promatrani ishod bila je smrtnost unutar 30 dana zbog plućne embolije. Sekundarni promatrani ishod bila je pojava kompliciranog kliničkog tijeka, definiranog eskalacijom terapije u obliku primjene kateholamina, trombolize ili embolektomije ili reanimacije.

Rezultati

Ukupno je 16 od 161 (9,9%) bolesnika umrlo u roku od 30 dana nakon prijema u bolnicu. Ispitanici koji su preminuli imali su značajno više razine TnI i CK-MB u plazmi, u usporedbi s

preživjelima. Pozitivan test H-FABP pronađen je kod 26 bolesnika, od kojih je njih 15 (57,7%) umrlo. Suprotno tome, jedan od 135 bolesnika s negativnim H-FABP je umro (0,7%, pozitivan H-FABP u odnosu na negativan P<0,001). Stratifikacija prema TnI rezultirala je pojavom smrtnosti od 19,7% (13 od 66) među TnI-pozitivnim pacijentima i 3,2% među onima koji su bili TnI-negativni (3 od 95; P=0,001). U ehokardiografiji, ispitanici s pozitivnim H-FABP pokazali su značajno veće RV/LV indekse u usporedbi s H-FABP negativnima (1,02 ± 0,21 u odnosu na 0,86 ± 0,22; P=0,001) i značajno niži TAPSE (13,7 ± 4,0 mm nasuprot 19,1 ± 4,7 mm; P<0,001). Nije bilo značajnih razlika za mTDI parametre. Multivarijantnom logističkom regresijskom analizom utvrđeni su H-FABP (OR=27,1; 95% CI 2,1 - 352,3), CK-MB (OR=5,3; 95% CI 1,3 - 23,3) i sistolički krvni tlak pri prijemu (OR=1,2 95% CI 1,1 - 1.3) kao neovisni prediktori 30-dnevne smrtnosti. Kombinacija pozitivnog H-FABP testa i povišenog CK-MB rezultirala je s posebno visokim rizikom od smrtnosti: umrlo je 14 od 16 bolesnika s ovom kombinacijom laboratorijskih nalaza (87,5%). Suprotno tome, vjerojatnost preživljavanja bolesnika s negativnim H-FABP testom iznosila je preko 99%.

Zabilježen je povećan rizik od kompliciranog kliničkog tijeka u bolesnika s pozitivnim H-FABP testom (OR=4,8; 95% CI 1,1- 21,1) i smanjenim TAPSE (OR=1,3; 95% CI 1,2 - 1,5). Bolesnici s vrijednostima TAPSE iznad 17,5 mm imali su nekompliciran tijek bolesti u 98% slučajeva.

Zaključak

Naši podaci podržavaju hipotezu da bi H-FABP mogao biti obećavajući prognostički biljeg za plućnu emboliju s intermedijarnim rizikom jer je snažno povezan s nepovoljnim kratkoročnim ishodom. Čini se da je njegova klinička vrijednost u stratifikaciji rizika veća od srčanih troponina. Kombinacija povišene razine H-FABP i CK-MB u plazmi ukazuje na posebno visok rizik od smrtnog ishoda. Klinička vrijednost CK-MB u stratifikaciji rizika od plućne embolije je nejasna i moguće podcijenjena te su potrebne daljnje studije. Povećane vrijednosti H-FABP koreliraju s ultrazvučnim markerima disfunkcije desne klijetke. MTDI nije pogodan za stratifikaciju rizika u ovoj skupini bolesnika. Potrebne su dodatne studije kako bi se utvrdilo koji su ultrazvučni parametri najkorisniji za procjenu rizika za smrtni ishod u bolesnika s akutnom plućnom embolijom srednjeg rizika.

8 Reference List

1. RLK V. Gesammelte Abhandlungen zur wissenschaftlichen Medicin: Von Meidinger und Sohn; 1856 1856. 1024 p.
2. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Archives of internal medicine. 2011;171(9):831-7. Epub 2011/05/11.
3. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379(9828):1835-46. Epub 2012/04/13.
4. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thrombosis and haemostasis. 2007;98(4):756-64. Epub 2007/10/17.
5. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). European heart journal. 2008;29(18):2276-315. Epub 2008/09/02.
6. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. Chest. 2002;122(4):1440-56. Epub 2002/10/16.
7. Konstantinides SV. Massive pulmonary embolism: what level of aggression? Seminars in respiratory and critical care medicine. 2008;29(1):47-55. Epub 2008/02/28.
8. Nakata T, Hashimoto A, Hase M, Tsuchihashi K, Shimamoto K. Human heart-type fatty acid-binding protein as an early diagnostic and prognostic marker in acute coronary syndrome. Cardiology. 2003;99(2):96-104. Epub 2003/04/25.
9. Viswanathan K, Kilcullen N, Morrell C, Thistlethwaite SJ, Sivananthan MU, Hassan TB, et al. Heart-type fatty acid-binding protein predicts long-term mortality and re-infarction in consecutive patients with suspected acute coronary syndrome who are troponin-negative. Journal of the American College of Cardiology. 2010;55(23):2590-8. Epub 2010/06/02.
10. Lankeit M, Kempf T, Dellas C, Cuny M, Tapken H, Peter T, et al. Growth differentiation factor-15 for prognostic assessment of patients with acute pulmonary embolism. American journal of respiratory and critical care medicine. 2008;177(9):1018-25. Epub 2008/02/12.

11. Dellas C, Puls M, Lankeit M, Schafer K, Cuny M, Berner M, et al. Elevated heart-type fatty acid-binding protein levels on admission predict an adverse outcome in normotensive patients with acute pulmonary embolism. Journal of the American College of Cardiology. 2010;55(19):2150-7. Epub 2010/05/08.
12. Stein PD, Janjua M, Matta F, Pathak PK, Jaweesh F, Alrifai A, et al. Prognosis based on creatine kinase isoenzyme MB, cardiac troponin I, and right ventricular size in stable patients with acute pulmonary embolism. The American journal of cardiology. 2011;107(5):774-7. Epub 2011/01/21.
13. Magder S. The left heart can only be as good as the right heart: determinants of function and dysfunction of the right ventricle. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2007;9(4):344-51. Epub 2007/12/07.
14. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: a major contributor to global disease burden. Arteriosclerosis, thrombosis, and vascular biology. 2014;34(11):2363-71. Epub 2014/10/12.
15. Heit JA. The epidemiology of venous thromboembolism in the community. Arteriosclerosis, thrombosis, and vascular biology. 2008;28(3):370-2. Epub 2008/02/26.
16. Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Kaptein AA, et al. Quality of life in long-term survivors of acute pulmonary embolism. Chest. 2010;138(6):1432-40. Epub 2010/05/25.
17. Fanikos J, Piazza G, Zayaruzny M, Goldhaber SZ. Long-term complications of medical patients with hospital-acquired venous thromboembolism. Thrombosis and haemostasis. 2009;102(4):688-93. Epub 2009/10/07.
18. Keller K, Hobohm L, Ebner M, Kresoja KP, Munzel T, Konstantinides SV, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. European heart journal. 2019. Epub 2019/05/19.
19. Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circulation research. 2016;118(9):1340-7. Epub 2016/04/30.
20. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Archives of internal medicine. 2000;160(6):809-15. Epub 2000/03/29.
21. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I9-16. Epub 2003/06/20.

22. Tapson VF. Acute pulmonary embolism. The New England journal of medicine. 2008;358(10):1037-52. Epub 2008/03/07.
23. Goldhaber SZ, Elliott CG. Acute pulmonary embolism: part I: epidemiology, pathophysiology, and diagnosis. Circulation. 2003;108(22):2726-9. Epub 2003/12/06.
24. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. The American journal of cardiology. 1971;28(3):288-94. Epub 1971/09/01.
25. Smulders YM. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. Cardiovascular research. 2000;48(1):23-33. Epub 2000/10/18.
26. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European heart journal. 2019. Epub 2019/09/11.
27. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest. 2002;121(3):877-905. Epub 2002/03/13.
28. Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jackle S, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation. 2002;106(10):1263-8. Epub 2002/09/05.
29. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation. 2003;107(20):2545-7. Epub 2003/05/14.
30. ten Wolde M, Tulevski, II, Mulder JW, Sohne M, Boomsma F, Mulder BJ, et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. Circulation. 2003;107(16):2082-4. Epub 2003/04/23.
31. Burrowes KS, Clark AR, Tawhai MH. Blood flow redistribution and ventilation-perfusion mismatch during embolic pulmonary arterial occlusion. Pulmonary circulation. 2011;1(3):365-76. Epub 2011/12/06.
32. Konstantinides S, Geibel A, Kasper W, Olschewski M, Blumel L, Just H. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. Circulation. 1998;97(19):1946-51. Epub 1998/06/03.
33. Kroegel C, Reissig A. Principle mechanisms underlying venous thromboembolism: epidemiology, risk factors, pathophysiology and pathogenesis. Respiration; international review of thoracic diseases. 2003;70(1):7-30. Epub 2003/02/14.

34. Tan P, Luscinskas FW, Homer-Vanniasinkam S. Cellular and molecular mechanisms of inflammation and thrombosis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 1999;17(5):373-89. Epub 1999/05/18.
35. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Archives of internal medicine. 2002;162(11):1245-8. Epub 2002/06/01.
36. Pollack CV, Schreiber D, Goldhaber SZ, Slattery D, Fanikos J, O'Neil BJ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). Journal of the American College of Cardiology. 2011;57(6):700-6. Epub 2011/02/05.
37. Miniati M, Prediletto R, Formichi B, Marini C, Di Ricco G, Tonelli L, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. American journal of respiratory and critical care medicine. 1999;159(3):864-71. Epub 1999/03/02.
38. Thames MD, Alpert JS, Dalen JE. Syncope in patients with pulmonary embolism. Jama. 1977;238(23):2509-11. Epub 1977/12/05.
39. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. European heart journal. 2019;40(11):902-10. Epub 2018/12/28.
40. Becattini C, Agnelli G, Lankeit M, Masotti L, Pruszczyk P, Casazza F, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. The European respiratory journal. 2016;48(3):780-6. Epub 2016/05/14.
41. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. Circulation. 2006;113(4):577-82. Epub 2006/01/25.
42. Becattini C, Agnelli G. Acute pulmonary embolism: risk stratification in the emergency department. Internal and emergency medicine. 2007;2(2):119-29. Epub 2007/07/11.
43. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-e96S. Epub 2012/02/15.

44. Kreit JW. The impact of right ventricular dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism. Chest. 2004;125(4):1539-45. Epub 2004/04/14.
45. Konstantinides S, Goldhaber SZ. Pulmonary embolism: risk assessment and management. European heart journal. 2012;33(24):3014-22. Epub 2012/09/11.
46. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thrombosis and haemostasis. 2000;83(3):416-20. Epub 2000/04/01.
47. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Annals of internal medicine. 2006;144(3):165-71. Epub 2006/02/08.
48. Sinha N, Yalamanchili K, Sukhija R, Aronow WS, Fleisher AG, Maguire GP, et al. Role of the 12-lead electrocardiogram in diagnosing pulmonary embolism. Cardiology in review. 2005;13(1):46-9. Epub 2004/12/15.
49. Schoepf UJ, Kucher N, Kipfmueller F, Quiroz R, Costello P, Goldhaber SZ. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. Circulation. 2004;110(20):3276-80. Epub 2004/11/10.
50. Perrier A, Desmarais S, Goehring C, de Moerloose P, Morabia A, Unger PF, et al. D-dimer testing for suspected pulmonary embolism in outpatients. American journal of respiratory and critical care medicine. 1997;156(2 Pt 1):492-6. Epub 1997/08/01.
51. Alpert JS, Smith R, Carlson J, Ockene IS, Dexter L, Dalen JE. Mortality in patients treated for pulmonary embolism. Jama. 1976;236(13):1477-80. Epub 1976/09/27.
52. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest. 1995;108(4):978-81. Epub 1995/10/01.
53. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet. 1960;1(7138):1309-12. Epub 1960/06/18.
54. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. The New England journal of medicine. 2014;370(15):1402-11. Epub 2014/04/11.
55. Digonnet A, Moya-Plana A, Aubert S, Flecher E, Bonnet N, Leprince P, et al. Acute pulmonary embolism: a current surgical approach. Interactive cardiovascular and thoracic surgery. 2007;6(1):27-9. Epub 2007/08/03.

56. Kuo WT, van den Bosch M, Hofmann LV, Louie JD, Kothary N, Sze DY. Catheter-directed embolectomy, fragmentation, and thrombolysis for the treatment of massive pulmonary embolism after failure of systemic thrombolysis. Chest. 2008;134(2):250-4. Epub 2008/08/07.

57. McIntyre KM, Sasahara AA. Determinants of right ventricular function and hemodynamics after pulmonary embolism. Chest. 1974;65(5):534-43. Epub 1974/05/01.

58. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mm Hg or higher. Archives of internal medicine. 2005;165(15):1777-81. Epub 2005/08/10.

59. Coutance G, Cauderlier E, Ehtisham J, Hamon M. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care. 2011;15(2):R103. Epub 2011/03/30.

60. Sanchez O, Trinquart L, Colombet I, Durieux P, Huisman MV, Chatellier G, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. European heart journal. 2008;29(12):1569-77. Epub 2008/05/23.

61. Becattini C, Agnelli G, Vedovati MC, Pruszczyk P, Casazza F, Grifoni S, et al. Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test. European heart journal. 2011;32(13):1657-63. Epub 2011/04/21.

62. O'Donoghue M, de Lemos JA, Morrow DA, Murphy SA, Buros JL, Cannon CP, et al. Prognostic utility of heart-type fatty acid binding protein in patients with acute coronary syndromes. Circulation. 2006;114(6):550-7. Epub 2006/08/02.

63. Kaczynska A, Pelsers MM, Bochowicz A, Kostrubiec M, Glatz JF, Pruszczyk P. Plasma heart-type fatty acid binding protein is superior to troponin and myoglobin for rapid risk stratification in acute pulmonary embolism. Clinica chimica acta; international journal of clinical chemistry. 2006;371(1-2):117-23. Epub 2006/05/16.

64. Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, et al. Increased human brain natriuretic peptide in congestive heart failure. The New England journal of medicine. 1990;323(11):757-8. Epub 1990/09/13.

65. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison

with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation. 1994;90(1):195-203. Epub 1994/07/01.

66. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation. 2003;108(18):2191-4. Epub 2003/11/05.
67. Coutance G, Le Page O, Lo T, Hamon M. Prognostic value of brain natriuretic peptide in acute pulmonary embolism. Crit Care. 2008;12(4):R109. Epub 2008/08/30.
68. Lankeit M, Jimenez D, Kostrubiec M, Dellas C, Kuhnert K, Hasenfuss G, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. The European respiratory journal. 2014;43(6):1669-77. Epub 2014/03/15.
69. Konstantinides S. Pulmonary embolism: impact of right ventricular dysfunction. Current opinion in cardiology. 2005;20(6):496-501. Epub 2005/10/20.
70. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation. 2007;116(4):427-33. Epub 2007/07/04.
71. Jimenez D, Uresandi F, Otero R, Lobo JL, Monreal M, Marti D, et al. Troponin-based risk stratification of patients with acute nonmassive pulmonary embolism: systematic review and metaanalysis. Chest. 2009;136(4):974-82. Epub 2009/05/26.
72. Boscheri A, Wunderlich C, Langer M, Schoen S, Wiedemann B, Stolte D, et al. Correlation of heart-type fatty acid-binding protein with mortality and echocardiographic data in patients with pulmonary embolism at intermediate risk. American heart journal. 2010;160(2):294-300. Epub 2010/08/10.
73. Baral R, Luo X, Watanabe H, Yamasawa I, Ibukiyama C. Role of MB isoforms (isomers) in the early diagnosis of acute myocardial infarction. Intern Med. 1994;33(4):210-5. Epub 1994/04/01.
74. Chin CT, Wang TY, Li S, Wiviott SD, deLemos JA, Kontos MC, et al. Comparison of the prognostic value of peak creatine kinase-MB and troponin levels among patients with acute myocardial infarction: a report from the Acute Coronary Treatment and Intervention Outcomes Network Registry-get with the guidelines. Clinical cardiology. 2012;35(7):424-9. Epub 2012/03/22.
75. Bagai A, Schulte PJ, Granger CB, Mahaffey KW, Christenson RH, Bell G, et al. Prognostic implications of creatine kinase-MB measurements in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. American heart journal. 2014;168(4):503-11 e2. Epub 2014/09/30.

76. Dohi T, Maehara A, Brener SJ, Genereux P, Gershlick AH, Mehran R, et al. Utility of peak creatine kinase-MB measurements in predicting myocardial infarct size, left ventricular dysfunction, and outcome after first anterior wall acute myocardial infarction (from the INFUSE-AMI trial). The American journal of cardiology. 2015;115(5):563-70. Epub 2015/01/15.

77. Bozbay M, Uyarel H, Avsar S, Oz A, Keskin M, Tanik VO, et al. Creatinine kinase isoenzyme-MB: A simple prognostic biomarker in patients with pulmonary embolism treated with thrombolytic therapy. Journal of critical care. 2015;30(6):1179-83. Epub 2015/08/25.

78. Ockner RK, Manning JA, Poppenhausen RB, Ho WK. A binding protein for fatty acids in cytosol of intestinal mucosa, liver, myocardium, and other tissues. Science. 1972;177(4043):56-8. Epub 1972/07/07.

79. Alhadi HA, Fox KA. Do we need additional markers of myocyte necrosis: the potential value of heart fatty-acid-binding protein. QJM : monthly journal of the Association of Physicians. 2004;97(4):187-98. Epub 2004/03/19.

80. Storch J, Thumser AE. The fatty acid transport function of fatty acid-binding proteins. Biochimica et biophysica acta. 2000;1486(1):28-44. Epub 2000/06/17.

81. van der Vusse GJ, Glatz JF, Stam HC. Myocardial fatty acid homeostasis. Molecular and cellular biochemistry. 1989;88(1-2):1-6. Epub 1989/06/24.

82. Glatz JF, van der Vusse GJ. Nomenclature of fatty acid-binding proteins. Molecular and cellular biochemistry. 1990;98(1-2):231-5. Epub 1990/10/08.

83. Azzazy HM, Pelsers MM, Christenson RH. Unbound free fatty acids and heart-type fatty acid-binding protein: diagnostic assays and clinical applications. Clinical chemistry. 2006;52(1):19-29. Epub 2005/11/05.

84. Lucke C, Rademacher M, Zimmerman AW, van Moerkerk HT, Veerkamp JH, Ruterjans H. Spin-system heterogeneities indicate a selected-fit mechanism in fatty acid binding to heart-type fatty acid-binding protein (H-FABP). The Biochemical journal. 2001;354(Pt 2):259-66. Epub 2001/02/15.

85. Pelsers MM, Hermens WT, Glatz JF. Fatty acid-binding proteins as plasma markers of tissue injury. Clinica chimica acta; international journal of clinical chemistry. 2005;352(1-2):15-35. Epub 2005/01/18.

86. Valle HA, Riesgo LG, Bel MS, Gonzalo FE, Sanchez MS, Oliva LI. Clinical assessment of heart-type fatty acid binding protein in early diagnosis of acute coronary syndrome.

European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2008;15(3):140-4. Epub 2008/05/08.

87. Niizeki T, Takeishi Y, Arimoto T, Nozaki N, Hirono O, Watanabe T, et al. Persistently increased serum concentration of heart-type fatty acid-binding protein predicts adverse clinical outcomes in patients with chronic heart failure. Circulation journal : official journal of the Japanese Circulation Society. 2008;72(1):109-14. Epub 2007/12/27.
88. Lankeit M, Dellas C, Panzenbock A, Skoro-Sajer N, Bonderman D, Olschewski M, et al. Heart-type fatty acid-binding protein for risk assessment of chronic thromboembolic pulmonary hypertension. The European respiratory journal. 2008;31(5):1024-9. Epub 2008/02/08.
89. Lindqvist P, Calcutteea A, Henein M. Echocardiography in the assessment of right heart function. European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology. 2008;9(2):225-34. Epub 2007/06/26.
90. McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. The American journal of cardiology. 1996;78(4):469-73. Epub 1996/08/15.
91. Galderisi M, Severino S, Cicala S, Caso P. The usefulness of pulsed tissue Doppler for the clinical assessment of right ventricular function. Italian heart journal : official journal of the Italian Federation of Cardiology. 2002;3(4):241-7. Epub 2002/05/25.
92. Gondi S, Dokainish H. Right ventricular tissue Doppler and strain imaging: ready for clinical use? Echocardiography. 2007;24(5):522-32. Epub 2007/04/26.
93. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Annals of internal medicine. 1999;130(6):461-70. Epub 1999/03/13.
94. Okamoto F, Sohmiya K, Ohkaru Y, Kawamura K, Asayama K, Kimura H, et al. Human heart-type cytoplasmic fatty acid-binding protein (H-FABP) for the diagnosis of acute myocardial infarction. Clinical evaluation of H-FABP in comparison with myoglobin and creatine kinase isoenzyme MB. Clinical chemistry and laboratory medicine. 2000;38(3):231-8. Epub 2000/07/25.
95. Schwarz W. Cardiodetect data sheet. Rennesens GmbH Berlin. 2010.
96. Miller D, Farah MG, Liner A, Fox K, Schluchter M, Hoit BD. The relation between quantitative right ventricular ejection fraction and indices of tricuspid annular motion

and myocardial performance. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2004;17(5):443-7. Epub 2004/05/04.

97. Ueti OM, Camargo EE, Ueti Ade A, de Lima-Filho EC, Nogueira EA. Assessment of right ventricular function with Doppler echocardiographic indices derived from tricuspid annular motion: comparison with radionuclide angiography. Heart. 2002;88(3):244-8. Epub 2002/08/16.

98. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. The New England journal of medicine. 2002;347(15):1143-50. Epub 2002/10/11.

99. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004;110(6):744-9. Epub 2004/07/21.

100. Dong BR, Hao Q, Yue J, Wu T, Liu GJ. Thrombolytic therapy for pulmonary embolism. The Cochrane database of systematic reviews. 2009(3):CD004437. Epub 2009/07/10.

101. Vuilleumier N, Le Gal G, Verschuren F, Perrier A, Bounameaux H, Turck N, et al. Cardiac biomarkers for risk stratification in non-massive pulmonary embolism: a multicenter prospective study. Journal of thrombosis and haemostasis : JTH. 2009;7(3):391-8. Epub 2008/12/18.

102. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Archives of internal medicine. 1998;158(6):585-93. Epub 1998/04/01.

103. Kostrubiec M, Labyk A, Pedowska-Wloszek J, Hrynkiewicz-Szymanska A, Pacho S, Jankowski K, et al. Mean platelet volume predicts early death in acute pulmonary embolism. Heart. 2010;96(6):460-5. Epub 2009/11/17.

104. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? Journal of the Royal Society of Medicine. 1989;82(4):203-5. Epub 1989/04/01.

105. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I4-8. Epub 2003/06/20.

106. Konstantinides S. [Diagnosis and therapy of pulmonary embolism]. VASA Zeitschrift fur Gefasskrankheiten. 2006;35(3):135-46. Epub 2006/08/31. Diagnostik und therapie der lungenembolie.

107. Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjonneland A, Overvad K. Anthropometry, body fat, and venous thromboembolism: a Danish follow-up study. Circulation. 2009;120(19):1850-7. Epub 2009/10/28.

108. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607. Epub 1988/12/01.

109. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010;121(17):1896-903. Epub 2010/04/21.

110. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2002;39(2 Suppl 1):S1-266. Epub 2002/03/21.

111. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international. 2005;67(6):2089-100. Epub 2005/05/11.

112. Escalon JC, Wong SS. False-positive cardiac troponin T levels in chronic hemodialysis patients. Cardiology. 1996;87(3):268-9. Epub 1996/05/01.

113. Gorski J, Hermens WT, Borawski J, Mysliwiec M, Glatz JF. Increased fatty acid-binding protein concentration in plasma of patients with chronic renal failure. Clinical chemistry. 1997;43(1):193-5. Epub 1997/01/01.

114. Kostrubiec M, Pruszczyk P, Bochowicz A, Pacho R, Szulc M, Kaczynska A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. European heart journal. 2005;26(20):2166-72. Epub 2005/05/25.

115. Jimenez D, Aujesky D, Moores L, Gomez V, Marti D, Briongos S, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax. 2011;66(1):75-81. Epub 2010/10/28.

116. Borrero S, Aujesky D, Stone RA, Geng M, Fine MJ, Ibrahim SA. Gender differences in 30-day mortality for patients hospitalized with acute pulmonary embolism. J Womens Health (Larchmt). 2007;16(8):1165-70. Epub 2007/10/17.

117. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation. 2008;117(13):1717-31. Epub 2008/04/02.

118. Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation. 2008;117(13):1711-6. Epub 2008/03/19.

119. Falga C, Capdevila JA, Soler S, Rabunal R, Sanchez Munoz-Torrero JF, Gallego P, et . Clinical outcome of patients with venous thromboembolism and renal insufficiency. Findings from the RIETE registry. Thrombosis and haemostasis. 2007;98(4):771-6. Epub 2007/10/17.

120. Adams JE, 3rd, Siegel BA, Goldstein JA, Jaffe AS. Elevations of CK-MB following pulmonary embolism. A manifestation of occult right ventricular infarction. Chest. 1992;101(5):1203-6. Epub 1992/05/01.

121. Gallotta G, Palmieri V, Piedimonte V, Rendina D, De Bonis S, Russo V, et al. Increased troponin I predicts in-hospital occurrence of hemodynamic instability in patients with sub-massive or non-massive pulmonary embolism independent to clinical, echocardiographic and laboratory information. International journal of cardiology. 2008;124(3):351-7. Epub 2007/03/27.

122. Beranek JT. MCC-135 diminishes the egress of CK-MB but not of troponin-I from cardiomyocytes during reperfusion. The Annals of thoracic surgery. 2005;79(3):1095; author reply Epub 2005/03/01.

123. Voss EM, Sharkey SW, Gernert AE, Murakami MM, Johnston RB, Hsieh CC, et al. Human and canine cardiac troponin T and creatine kinase-MB distribution in normal and diseased myocardium. Infarct sizing using serum profiles. Archives of pathology & laboratory medicine. 1995;119(9):799-806. Epub 1995/09/01.

124. Swaanenburg JC, Visser-VanBrummen PJ, DeJongste MJ, Tiebosch AT. The content and distribution of troponin I, troponin T, myoglobin, and alpha-hydroxybutyric acid dehydrogenase in the human heart. American journal of clinical pathology. 2001;115(5):770-7. Epub 2001/05/11.

125. Becattini C, Lignani A, Masotti L, Forte MB, Agnelli G. D-dimer for risk stratification in patients with acute pulmonary embolism. Journal of thrombosis and thrombolysis. 2012;33(1):48-57. Epub 2011/11/24.

126. Stein PD, Janjua M, Matta F, Alrifai A, Jaweesh F, Chughtai HL. Prognostic value of D-dimer in stable patients with pulmonary embolism. Clinical and applied

thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2011;17(6):E183-5. Epub 2011/02/04.

127. Holley AB, Cheatham JG, Jackson JL, Moores LK, Villines TC. Novel quantitative echocardiographic parameters in acute PE. Journal of thrombosis and thrombolysis. 2009;28(4):506-12. Epub 2009/03/14.

128. Rydman R, Larsen F, Caidahl K, Alam M. Right ventricular function in patients with pulmonary embolism: early and late findings using Doppler tissue imaging. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2010;23(5):531-7. Epub 2010/04/13.

129. Saxena N, Rajagopalan N, Edelman K, Lopez-Candales A. Tricuspid annular systolic velocity: a useful measurement in determining right ventricular systolic function regardless of pulmonary artery pressures. Echocardiography. 2006;23(9):750-5. Epub 2006/09/27.

130. Rodrigues AC, Guimaraes L, Guimaraes JF, Monaco C, Cordovil A, Lira E, et al. Relationship of clot burden and echocardiographic severity of right ventricular dysfunction after acute pulmonary embolism. The international journal of cardiovascular imaging. 2015;31(3):509-15. Epub 2014/11/28.

131. Tuller D, Steiner M, Wahl A, Kabok M, Seiler C. Systolic right ventricular function assessment by pulsed wave tissue Doppler imaging of the tricuspid annulus. Swiss medical weekly. 2005;135(31-32):461-8. Epub 2005/10/07.

132. Karbek B, Ozbek M, Bozkurt NC, Ginis Z, Gungunes A, Unsal IO, et al. Heart-type fatty acid binding protein (H-FABP): relationship with arterial intima-media thickness and role as diagnostic marker for atherosclerosis in patients with impaired glucose metabolism. Cardiovascular diabetology. 2011;10:37. Epub 2011/05/04.

133. Puls M, Dellas C, Lankeit M, Olschewski M, Binder L, Geibel A, et al. Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism. European heart journal. 2007;28(2):224-9. Epub 2006/11/28.

134. Chan CP, Sum KW, Cheung KY, Glatz JF, Sanderson JE, Hempel A, et al. Development of a quantitative lateral-flow assay for rapid detection of fatty acid-binding protein. Journal of immunological methods. 2003;279(1-2):91-100. Epub 2003/09/13.

135. Scridon T, Scridon C, Skali H, Alvarez A, Goldhaber SZ, Solomon SD. Prognostic significance of troponin elevation and right ventricular enlargement in acute pulmonary embolism. The American journal of cardiology. 2005;96(2):303-5. Epub 2005/07/16.

136. Stein PD, Matta F, Janjua M, Yaekoub AY, Jaweesh F, Alrifai A. Outcome in stable patients with acute pulmonary embolism who had right ventricular enlargement and/or elevated levels of troponin I. The American journal of cardiology. 2010;106(4):558-63. Epub 2010/08/10.

137. Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. Lancet. 1998;351(9109):1077-80. Epub 1998/07/11.

138. Pruszczyk P, Goliszek S, Lichodziejewska B, Kostrubiec M, Ciurzynski M, Kurnicka K, et al. Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism. JACC Cardiovascular imaging. 2014;7(6):553-60. Epub 2014/01/15.

139. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. American journal of respiratory and critical care medicine. 2006;174(9):1034-41. Epub 2006/08/05.

140. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation. 2000;101(24):2817-22. Epub 2000/06/22.

141. Platz E, Hassanein AH, Shah A, Goldhaber SZ, Solomon SD. Regional right ventricular strain pattern in patients with acute pulmonary embolism. Echocardiography. 2012;29(4):464-70. Epub 2012/01/27.

142. Sugiura E, Dohi K, Onishi K, Takamura T, Tsuji A, Ota S, et al. Reversible right ventricular regional non-uniformity quantified by speckle-tracking strain imaging in patients with acute pulmonary thromboembolism. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2009;22(12):1353-9. Epub 2009/10/20.

143. Khemasuwan D, Yingchoncharoen T, Tunsupon P, Kusunose K, Moghekar A, Klein A, et al. Right ventricular echocardiographic parameters are associated with mortality after acute pulmonary embolism. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2015;28(3):355-62. Epub 2015/01/07.

144. Lee K, Kwon O, Lee EJ, Sin MJ, Lee JS, Lee S, et al. Prognostic value of echocardiographic parameters for right ventricular function in patients with acute non-

massive pulmonary embolism. Heart and vessels. 2019;34(7):1187-95. Epub 2019/01/24.

9 Publications

1. Heart-type fatty acid-binding protein and myocardial creatine kinase enable rapid risk stratification in normotensive patients with pulmonary embolism. Langer M*, **Forkmann M***, Richter U, Tausche AK, Sveric K, Christoph M, Ibrahim K, Günther M, Kolschmann S, Boscheri A, Barthel P, Strasser RH, Wunderlich C. (*contributed equally) *J Crit Care.* 2016 May 26; 35:174-179. (**IF 2.44**) - Full Paper
2. Update catherablation – Catheterablation in supraventricular tachycardia. **Forkmann M,** Schwab C, Busch S. *Herzschrittmacherther Elektrophysiol*. Herzschrittmacherther Elektrophysiol. 2019 Dec;30(4):336-342 - Review
3. Characteristics of early recurrences detected by continuous cardiac monitoring influencing the long-term outcome after atrial fibrillation ablation. **Forkmann M**, Schwab C, Edler D, Vevecka A, Butz S, Haller B, Brachmann J, Busch S. *J Cardiovasc Electrophysiol.* 2019 Oct;30(10):1886-1893 (**IF 2.873**) – Full paper
4. Predictive Factors and Safety of Noninvasive Mechanical Ventilation in Combination With Propofol Deep Sedation in Left Atrial Ablation Procedures. Vevecka A, Schwab C, **Forkmann M**, Butz S, Issam A, Turschner O, Mahnkopf C, Brachmann J, Busch S. *Am J Cardiol.* 2019 Jul 15;124(2):233-238 (**IF 2.843**) – Full Paper
5. Stored red blood cells impair vascular function in vivo. **Forkmann M,** Christoph M, Ibrahim K, Swoboda M, Kolschmann S, Strasser RH, Wunderlich C. *Transfusion.* 2014 Jan;54(1):255 (**IF 3.042**) – Research Letter
6. Acute and long-term outcome of focal atrial tachycardia ablation in the real world: results of the german ablation registry. Busch S, **Forkmann M**, Kuck KH, Lewalter T, Ince H, Straube F, Wieneke H, Julian Chun KR, Eckardt L, Schmitt C, Hochadel M, Senges J, Brachmann J. *Clin Res Cardiol.* 2018 May;107(5):430-436 (**IF 4.32**) - Full Paper
7. Conventional mapping and ablation of focal VT in the healthy heart. Busch S, Brachmann J, Saleh A, **Forkmann M**. *Herzschrittmacherther Elektrophysiol*. 2017 Jun;28(2):187-192- Review
8. Reduction of atrial fibrillation burden by pulmonary vein isolation leads to a decrease of CD11b expression on inflammatory cells. Tarnowski D, Plichta L, **Forkmann M**, Quick S, Ulbrich S, Heidrich FM, Wiedemann S, Christoph M, Poitz DM, Wunderlich C, Ibrahim K, Strasser RH, Pfluecke C. *Europace*. 2017 Jan 10 **(IF 4.021)** - Full Paper

9. Total atrial conduction time to predict occult atrial fibrillation after cryptogenic stroke. Müller P, Ivanov V, Kara K, Klein-Wiele O, **Forkmann M**, Piorkowski C, Blockhaus C, Dimitroulis D, Afzal S, Shin DI, Kelm M, Makimoto H, Mügge A. *Clin Res Cardiol*. 2017 Feb;106(2):113-119 (**IF 4.32**) - Full Paper
10. Association of platelet activation markers with recurrence of atrial fibrillation after pulmonary vein isolation. Pfluecke C, Plichta L, Tarnowski D, **Forkmann M**, Ulbrich S, Quick S, Heidrich FM, Wiedemann S, Christoph M, Poitz DM, Wunderlich C, Strasser RH, Ibrahim K. *Platelets*. 2016 Oct 13:1-6. (**IF 3.213**) - Full Paper
11. Target temperature management of 33 °C exerts beneficial hemodynamic effects after out of hospital cardiac arrest. **Forkmann M.**, Kolschmann S, Holzhauser L, Ibrahim K., Guenther M., Christoph M., Fuhrmann JT., Boscheri A, Schmeißer A, Strasser RH., Wunderlich C. *Acta Cardiologica* 2015, Aug; 70(4):451-9 (**IF 0.6**) - Full Paper
12. Reduction of fluoroscopy exposure during atrial fibrillation ablation using a novel fluoroscopy image integrated 3-dimensional electroanatomical mapping system: A prospective, randomized, single-blind, and controlled study. Huo Y, Christoph M, **Forkmann M**, Pohl M, Mayer J, Salmas J, Sitzy J, Wunderlich C, Piorkowski C, Gaspar T. *Heart Rhythm*. 2015 May 19. (**IF 4.39**) - Full Paper
13. Epicardial Ventricular Tachycardia Ablation in a Patient With Brugada ECG Pattern and Mutation of PKP2 and DSP Genes. **Forkmann M**, Tomala J, Huo Y, Mayer J, Christoph M, Wunderlich C, Salmas J, Gaspar T, Piorkowski C. *Circ Arrhythm Electrophysiol*. 2015 Apr;8(2):505-7 (**IF 5.947**) – Case report
14. Fluoroscopy integrated 3D mapping significantly reduces radiation exposure during ablation for a wide spectrum of cardiac arrhythmias. Christoph M, Wunderlich C, Moebius S, **Forkmann M**, Sitzy J, Salmas J, Mayer J, Huo Y, Piorkowski C, Gaspar T. *Europace*. 2015 Jun;17(6):928-37 (**IF 4.021**) - Full Paper
15. Intra-aortic balloon pump (IABP) counterpulsation improves cerebral perfusion in patients with decreased left ventricular function. Pfluecke C, Christoph M, Kolschmann S, Tarnowski D, **Forkmann M**, Jellinghaus S, Poitz DM, Wunderlich C, Strasser RH, Schoen S, Ibrahim K. *Perfusion*. 2014 Nov;29(6):511-6. (**IF 1.442**) - Full Paper
16. As compared to allopurinol, urate-lowering therapy with febuxostat has superior effects on oxidative stress and pulse wave velocity in patients with severe chronic tophaceous gout. Tausche AK, Christoph M, **Forkmann M**, Richter U, Kopprasch S, Bielitz C, Aringer M, Wunderlich C. *Rheumatol Int*. 2014 Jan;34(1):101-9. (**IF 1.702**) - Full Paper

17. Dexrazoxane prevents the development of the impaired cardiac phenotype in caveolin-1-disrupted mice. Polanski AK, Ebner A, Ebner B, Hofmann A, Steinbronn N, Brandt A, **Forkmann M**, Tausche AK, Morawietz H, Strasser RH, Wunderlich C. *J Cardiovasc Pharmacol.* 2013 Jun;61(6):545-52. (**IF 2.462**) - Full Paper
18. Impending paradoxical thromboembolism: thrombus caught in transit. A case report. **Forkmann M**, Tugtekin SM, Strasser RH, Schrötter H. *Clin Res Cardiol.* 2012 Feb 2. (**IF 4.32**) – Case report
19. Nitric oxide synthases are crucially involved in the development of the severe cardiomyopathy of caveolin-1 knockout mice. Wunderlich C, Schober K, Heerwagen C, Marquetant R, Ebner B, **Forkmann M**, Schoen S, Braun-Dullaeus RC, Schmeisser A, Strasser RH. *Biochem Biophys Res Commun*. 2008 Dec 19;377(3):769-74. (**IF 2.484**) - Full Paper

Curriculum Vitae

Mathias Forkmann

address:	Rotdornweg 1 96450 Coburg Germany
phone number:	+49 / 9561 / 22 33233
mobile number:	+49/ 179/ 2105697
e-mail:	mathias.forkmann@gmx.net

Personal Details

date of birth:	September 30th, 1980
place of birth:	Schkeuditz, Germany
marital status:	married, 3 children
nationality:	german

Education and Qualification

08/1987 – 06/1992	Elementary School in Hartmannsdorf
08/1992 – 06/1999	Gymnasium Burgstädt 06/1999: German University entrance qualification Examination (Abitur)
09/1999 – 11/2005	University of Leipzig, Germany Medical School 11/2005: final exam of medical studies

---

Professional Qualifications

12/2005	License to practice regional board Chemnitz, Germany
10/2012	Specialist in Internal Medicine and Cardiology

10/2014	Specialist in invasive electrophysiology and active cardiac device implantation
01/2021	Specialist in heart failure medicine

Work experience

04/2006 to 12/2012	Assistant physician Department of Cardiology Heart Centre Dresden, University of Dresden Fetscherstr. 76 01307 Dresden Germany
01/2013 to 03/2016	Consultant Department of Electrophysiology Heart Centre Dresden, University of Dresden Fetscherstr. 76 01307 Dresden Germany
04/2016 to present	Senior physician Department of Cardiology Klinikum Coburg Ketschendorfer Strasse 33 96450 Coburg Germany

---

Research

09/2007	Doctoral Thesis: “Differential extracellular matrix gene expression in human aortic diseases: Significance of matrix metalloproteinases” Department of Cardiac Surgery, Heart Center, University of Leipzig, Leipzig, Germany
04/15 to 05/15	Research Fellowship on the Department of Cardiology – Arrhythmia Section – Hospital Clinic Barcelona, Spain
12/14 to 04/16	Fellowship „Heart Rhythm“ (Boston Scientific)

01/18 to 05/21	Doctor of Science, In area: Biomedicine and health, Field: Clinical medical sciences, Branch: Internal medicine. University of Split, School of Medicine “Clinical benefits and prognostic value of Heart-Type Fatty Acid binding protein, myocardial creatine kinase and specific right ventricular echocardiographic parameters for risk stratification of normotensive patients with pulmonary embolism”

Languages

German	Mother tongue
English	Oral and written

Clinical trials experience

Efficacy of DE-MRI-Guided Ablation vs. Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II) – since October 2016

Preventive aBlation of vEntricular tachycaRdia in Patients With myocardiaL INfarction (BERLIN VT) – since July 6, 2015

Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy (AXAFA – AFNET 5) – EHJ 2018; 39(32):2942-2955

Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) – JAMA 2019; 321(13):1261-1274

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS HF) - N Engl J Med 2011; 364:11-21January 6, 2011

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) – published N Engl J Med 2011; 365:883-891September 8, 2011