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# **RIGHT VENTRICULAR FUNCTION IN PULMONARY EMBOLISM**

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To my father



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## ABSTRACT

Patients with pulmonary embolism (PE) and right ventricular (RV) dysfunction are known to be at risk of in-hospital clinical worsening and PE-related mortality. Even in patients with a preserved systemic arterial pressure, the RV dysfunction indicates a higher risk, thus affecting the patients' level of care and the therapeutic approach. Involvement of the right ventricle is usually associated with at least a moderate degree of PE. The extent of the pulmonary vascular obstruction has been shown to be crucial for the increase in pulmonary vascular resistance and, thereby, for the prognosis of the patients. A substantially elevated D-dimer in clinically suspected patients is suggestive of PE and is associated with an adverse outcome. Echocardiography is frequently used to assess RV function in PE patients. The pulsed-wave Doppler tissue imaging (DTI) technique has been used to detect RV dysfunction in different clinical conditions and has been validated by several non-invasive techniques. The aim of these studies was to investigate the role of RV dysfunction detected by echocardiographic techniques in PE patients and to relate the findings to D-dimer levels, the extent of perfusion loss detected by pulmonary scintigraphy, and clinical prediction rules.

**Study I:** By using tricuspid annular plane excursion, both systolic and diastolic RV functions were found to be impaired in the acute stage and, to an even higher degree, in association with an elevated RV systolic pressure. Diastolic function recovered earlier than systolic function.

**Study II:** Using DTI technique, disturbed diastolic RV function was identified in patients with normal RV systolic pressure, normal RV systolic function and normal filling pressure.

**Study III:** A cut-off value for the D-dimer level was found to identify patients with RV dysfunction. Patients with higher D-dimer levels also had higher pulmonary vascular resistance and RV systolic pressure.

**Study IV:** Signs of RV dysfunction were detected even in patients with relatively small lung perfusion losses. Lung perfusion had good correlation with pulmonary vascular resistance.

**Conclusion:** Non-high-risk PE patients show signs of disturbed RV function. Diastolic RV function seems to be affected earlier than systolic RV function, as detected by the DTI-derived tricuspid early diastolic velocity (Em), indicating that this parameter can be used to detect RV dysfunction even in patients with normal systolic RV pressure at presentation. Also, a certain D-dimer level and degree of lung perfusion loss may be useful in identifying non-high-risk PE patients who should be further investigated and monitored.

## LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original papers which are referred to by their Roman numerals.

- I. Rydman R, Söderberg M, Larsen F, Caidahl K, Alam M.  
Echocardiographic evaluation of right ventricular function in patients with acute pulmonary embolism: a study using tricuspid annular motion.  
*Echocardiography* 2010;27:286-93.
- II. 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* 2010;23:531-7.
- III. Rydman, R, Söderberg M, Larsen F, Alam M, Caidahl K.  
D-dimer and pulmonary embolism severity index in relation to right ventricular function.  
*Manuscript*.
- IV. Rydman, R, Bone D, Alam M, Caidahl K, Larsen F.  
Right ventricular function with reference to perfusion determined by pulmonary scintigraphy in acute pulmonary embolism.  
*Manuscript*.

## LIST OF ABBREVIATIONS

A	Atrial transmitral peak flow velocity
Am	Late diastolic myocardial velocity
BMI	Body mass index
CMR	Cardiac magnetic resonance imaging
CT	Cardiac computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography of the pulmonary arteries
2D	2-dimensional
3D	3-dimensional
DTI	Doppler tissue imaging
DVT	Deep vein thrombosis
E	Early transmitral peak flow velocity
Em	Early diastolic myocardial velocity
ET	Ejection time
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time
LV	Left ventricular
MAM	Mitral annular motion
MDCT	Multidetector cardiac computed tomography
MPI	Myocardial performance index
PA	Pulmonary angiography
PE	Pulmonary embolism
PESI	Pulmonary embolism severity index
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
ROC	Receiver- operating characteristic curves
RV	Right ventricular
RVEDd	Right ventricular end-diastolic dimension
RVEF	Right ventricular ejection fraction
RVFAC	Right ventricular area contraction
Sm	Peak systolic myocardial velocity
SPECT	Single photon emission computed tomography
STE	Speckle tracking echocardiography
TAPDE	Tricuspid annular plane diastolic excursion
TAPSE	Tricuspid annular plane systolic excursion
TAV	Tricuspid annular velocity
TR	Tricuspid regurgitation
TRV	Tricuspid regurgitation velocity
TVI <sub>rvot</sub>	Right ventricular outflow tract time-velocity integral
VTE	Venous thromboembolism
V/Q	Ventilation Perfusion
WU	Wood Units



# 1 INTRODUCTION

## 1.1 Background

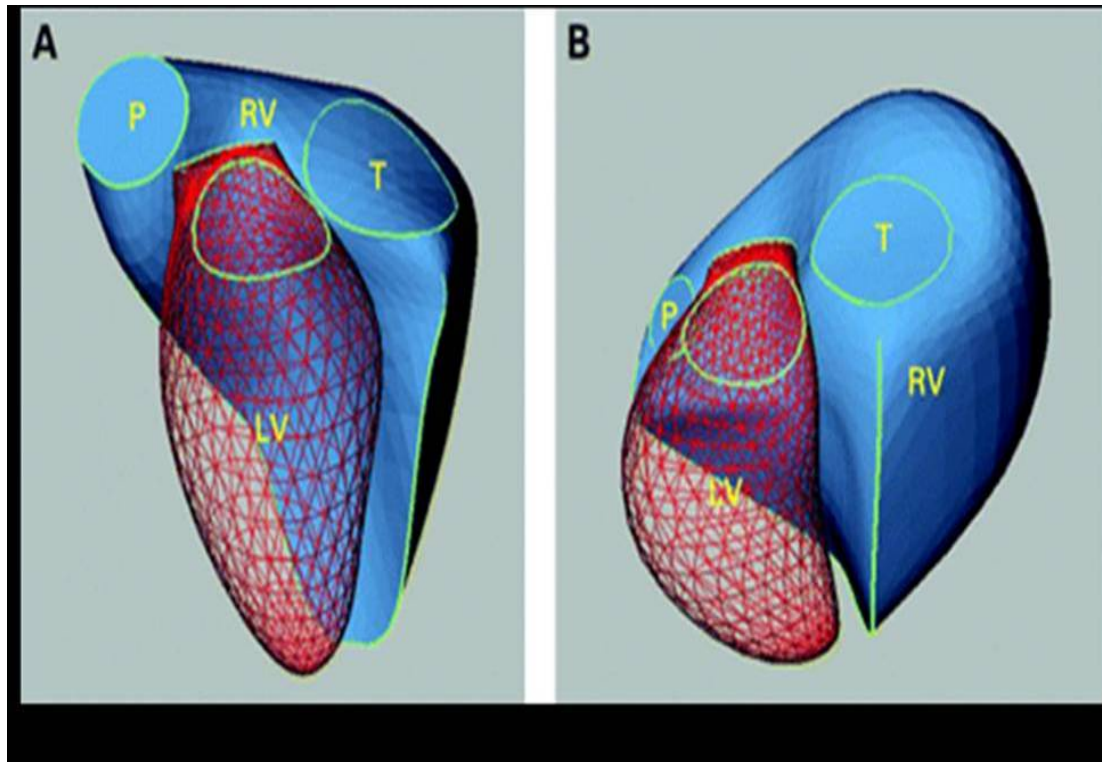
### 1.1.1 Right Ventricle

The right ventricle has a triangular shape when viewed from the side and a more crescent-like appearance in cross-section. Traditionally, it has been divided into a conus, or outflow tract, and a sinus, or body of the right ventricle. This was based on the work by Keith in the 1920s, demonstrating the bulbus cordis as a separate chamber distal to the common ventricle in the developing embryo, and forming the infundibulum, or outflow tract (1). The right ventricle is derived from the anterior heart field, whereas the left ventricle and the atrial chambers are derived from the primary heart field (2). Interestingly, in the left ventricle, the bulbus disappears during development explaining the absence of an infundibular component as well as mitral-aortic continuity (1). Studies on knockout mice and the discovery of transcription factors HAND1 and HAND2 led to the recognition of chamber-specific heart formation (3). More recently, especially for congenital heart disease, the right ventricle is often divided into three parts: an inlet portion containing the tricuspid valve apparatus, a subpulmonary outlet portion, and a trabeculated apical portion (4-5).

Both cardiac ventricles are composed of multiple muscle layers forming a single functional unit. The superficial muscle layers in the sinus portion of the right ventricle are directly continuous with superficial layers of the left ventricle, whereas fibre bundles in deeper layers are continuous with those of the interventricular septum (1). The interventricular septum is generally considered to be part of the left ventricle, but it contains longitudinal fibres belonging to the right ventricle. The configuration of subendocardial and subepicardial fibre pathways can be described as a figure-eight pattern creating a strong interdependence between the right and left ventricles (6). Since the right ventricle lacks the middle layer of circumferential fibres found in the left ventricle, it relies more heavily on the longitudinal shortening (7).

In the right ventricle, the interaction of three different sources, the RV free wall, the interventricular septum, and the conus, contributes to the ejection. The interventricular septum is concave towards the left ventricle in both systole and diastole under normal loading conditions.

The right ventricle requires a lower filling pressure to reach the same sarcomere length as the left ventricle. The amount of force that can be generated is proportional to the length of the sarcomere; when stretched beyond the maximum length the force diminishes. RV pressure



**Figure 1.** 3-dimensional reconstruction of the right ventricle (RV) illustrating its complex shape in normal subject (A), and in remodeled, diseased heart, with profound change in shape (B). The mesh surface is the left ventricle (LV). P - pulmonary valve; T – tricuspid valve. Reproduced from Heart, Sheehan and Reddington, 94:1510-15, 2008 with permission from BMJ Publishing Group Ltd.

tracings show an early peaking and rapidly declining pressure (8). Because of the low pulmonary artery diastolic pressure, there is very little isovolumic contraction. The first part of the RV ejection is due to a reduction in free wall surface area and septal-to-free wall distance by active shortening of the myofibrils. At the end of systole blood located in the RV outflow tract continues to flow forward despite the presence of declining pressure and even a negative pressure gradient, most likely due to blood momentum (1, 8-10). A longer duration of thickening of the interventricular septum compared with the RV free wall could contribute to late shortening in the septal-to-free wall dimension. The temporal separation between peak pressure and end-ejection is probably due to the low-impedance, highly compliant pulmonary circulation. Under normal conditions, the RV outflow tract begins to contract about 25-50 msec later and remains contracted longer than the rest of the right ventricle (1, 11). This temporal

difference can be exaggerated by vagal stimulation or abolished by sympathetic stimulation (1). 3D strain imaging has demonstrated a sequential RV contraction with inward movement of the RV free wall creating a bellows-like effect, contraction of the longitudinal fibres leading to the long axis shortening, and bulging of the interventricular septum into the RV cavity (12). The longitudinally arranged muscle fibres in the supraventricular crest extend from the interventricular septum and out along the tricuspid annulus and RV free wall, thus facilitating the inward motion of the free wall while integrating the contraction of the right and left ventricles (13). Under normal loading conditions, there is little short axis thickening, rotation and twisting (14-17).

Despite the fact that the RV wall thickness is only about one-third of the LV wall thickness, the cardiac output is approximately the same for the right and left ventricle, with some physiological shunting for the bronchial vessels, but it is achieved with a myocardial energy cost of about one-fifth of that of the left ventricle. This is partly explained by the comparatively low RV pressure system due to the mean pulmonary artery pressure and the pulmonary vascular resistance being about one-sixth of their systemic counterparts, which is made possible by the thin-walled pulmonary arteries with similar stiffness between central and peripheral sites resulting in more distensible arteries than in the systemic circulation. Also, the pulmonary pulse pressure is lower and there are no well-developed arterioles in the pulmonary circulation. The pulse wave velocity is about one-half of that of the systemic circulation, causing reflected pressure waves to return later after pulmonic valve closure, which optimally matches the right and left ventricles at physiological heart rates (18).

In accordance with Starling's law, the right ventricle can respond to an acute increase in its workload by dilating. When an increased workload is imposed for a longer period of time the right ventricle hypertrophies - an adaptation that increases its capacity to work. In the normal heart, the right ventricle dilates more rapidly than blood can enter the ventricular cavity, thereby creating a diastolic suction that augments RV filling, being, as it is, a more important component than the late diastolic atrial contraction. Both mechanisms are of greater importance in a diseased right ventricle. The characteristics of RV contraction are primarily dependent on its loading conditions.

Pressure-volume loops can facilitate understanding of the complex relationship between RV contractility, preload, and afterload because they depict instantaneous pressure-volume loops under different loading conditions. The unique characteristics of the human RV pressure-volume relationship were demonstrated recently as having a triangular or trapezoidal form with ill-defined periods of isovolumic contraction and, particularly, isovolumic relaxation (9). Many

investigators consider time-varying maximal RV ventricular elastance to be the most reliable index of RV contractility (19). Changes in maximal elastance were noted with changes in inotropy, with the slope of maximum pressure/volume being linear over a wide range of boundary conditions (20). There are, however, some limitations to this model, such as variability in slope values, and afterload dependency (21). According to the Frank-Starling mechanism, an increase within physiological limits in RV preload improves myocardial contraction. Several factors, such as heart rate, ventricular relaxation and compliance, intravascular volume status, atrial characteristics, LV filling and pericardial constraint, influence RV filling (22). The ventricular filling period is an important determinant of ventricular preload and function. The right ventricle follows a force-interval relationship in which stroke volume increases above baseline after longer filling periods, as seen in postextrasystolic beats (23). The right ventricle has a high sensitivity to afterload change. Although one of the most frequently used indices of RV afterload in clinical practice, pulmonary vascular resistance may not reflect the complex nature of ventricular afterload. Ideally, the static and dynamic components of pulmonary vascular impedance and valvular or intracavitary resistive components would be accounted for (1, 24).

The influence of the mechanical work of breathing has a major impact on beat-by-beat and breath-by-breath right heart haemodynamics. The small change in intrapleural pressure during inspiration leads to an increase in venous return and RV preload and accounts for the changes in RV stroke volume during respiration (14).

The two ventricles share the pericardium, and have common myofibres, particularly in the superficial layer. Ventricular interaction occurs during both systole and diastole. Ventricular interdependence is most apparent with changes in loading conditions such as those seen with respiration and sudden postural changes (25). The normal geometry of the right ventricle, wrapped around the left ventricle in its short axis, produces RV shortening, as well as a transseptal contribution to RV pressure generation. An experimental study on electrically isolated ventricles in an otherwise intact heart showed that about 30% of the contractile energy of the right ventricle was generated by the left ventricle (26). In the presence of an intact pericardium, acute RV dilatation interferes with LV contractile performance. Thus, an intact pericardium ensures ventricular interaction. If the pericardium is removed, ventricular interaction persists but is attenuated (27). The evidence for diastolic ventricular interdependence is based on many experimental and clinical studies and relates to the effects of distension of one ventricle to the contralateral chamber. A progressive increase in RV end-diastolic volume was seen between low and high pressures resulting largely from an increase in the distance between

the RV septum and free wall (25, 28). Under normal conditions, the intrapericardial pressure is the same as the intrathoracic pressure, ranging from – 3 to – 6 mm Hg on expiration and inspiration, respectively. Changes in the intrapericardial pressure produce alterations in the ventricular transmural pressure. RV diastolic dysfunction adversely affects LV diastolic properties through interactions mediated by the reversed curved septum and exacerbated by elevated intracardial pressure.

The right ventricle functions at low oxygen demands and pressure. It is perfused both in systole and diastole, and its ability to extract oxygen is increased during haemodynamic stress. These factors make the right ventricle less susceptible to infarction than the left ventricle. With normal aging, the pulmonary artery pressure and pulmonary vascular resistance increase mildly, secondary to an increase in arterial stiffness of the pulmonary vasculature (29-30). RV diastolic function changes over time, whereas the systolic function is less affected (31-32).

## **1.2. Methods for RV evaluation**

Right ventricular assessments are challenging due to the complex 3-dimensional geometric structure of the ventricle, the limited definition of endocardial borders caused by extensive myocardial trabeculation, the retrosternal position, the marked load dependence of indices of RV function, and the interrelationship with the left ventricle (33). Many imaging and functional modalities are available for RV studies. Cardiac magnetic resonance imaging (CMR) is being used increasingly as a standard tool but, in clinical practice, echocardiography is still the most widely used modality. Other modalities include radionuclide-based methods, tomography methods and cardiac catheterization.

### **1.2.1 Echocardiography**

Compared with other modalities, echocardiography offers the advantage of availability and versatility. It is by far the most mobile of the current modalities. Most of the echocardiographic methods purposed for assessing of RV function are based on volumetric approximations of the right ventricle. Considering the complex RV anatomy, these models only crudely represent the true RV volume (34-35). The outflow portion of the right ventricle may account for up to 25% of the total RV volume (36). The RV inflow and outflow tracts are positioned in different planes, which make them difficult to portray simultaneously with 2D techniques. There are several different variables that can be used to assess RV systolic and diastolic function,

including methods based on 2D- or 3D-echocardiography, blood-pool Doppler ultrasound, tissue Doppler ultrasound and myocardial deformation.

For qualitative evaluation of the right ventricle, the RV size is often compared to the LV size, which is normally two-thirds the size of the left ventricle and the global RV systolic function is determined by subjective eyeballing assessment. Several echocardiographic projections should be used to assess the whole of the right ventricle with its specific regional landmarks, and to avoid false positive findings. McConnell et al. (37) reported a segmental RV dysfunction in patients with pulmonary embolism (PE), and others have described distinct segmental patterns in RV dysfunction in different diseases such as acute RV myocardial infarction and arrhythmogenic RV dysplasia (38-39). Qualitative eyeballing to determine the global and regional RV function may be satisfactory when performed by a highly experienced echocardiographer, but it is limited by the not negligible interobserver variability, especially in conjunction with significant tricuspid and/or pulmonary regurgitation.

A quantitative approach should be attempted for better accuracy, serial assessments, and for comparisons with reference values. In clinical practice, the RV ejection fraction (RVEF) is the most frequently used index of RV contractility. As no reliable calculations of the RVEF using 2D echocardiography is possible, surrogate parameters have been proposed.

RV fractional area contraction (RVFAC) can be used to determine the RV ejection fraction and has shown to have good correlation with CMR-derived RVEF (40), but it presents a major challenge to accurately trace the RV endocardial borders, especially around the trabeculated apex. RVFAC has been shown to have prognostic value in pulmonary hypertension, myocardial infarction, and in patients undergoing cardiac surgery (41-43).

Tricuspid annular plane systolic excursion (TAPSE) has been used to study RV dysfunction in different cardiac diseases, and it has been shown to be of prognostic value in advanced heart failure, myocardial infarction, and in pulmonary artery hypertension (44-46). TAPSE reflects the longitudinal systolic movement of the tricuspid annulus towards the apex and has been shown to be closely related to the RV ejection fraction and RVFAC (47). TAPSE is recorded from the lateral tricuspid annulus in the four-chamber view by M-mode imaging, it is easy to measure and has shown good reproducibility (46).

Doppler tissue imaging (DTI) allows direct measurement of low systolic and diastolic myocardial velocities (48-50). The analysis by pulsed-wave DTI technique is usually performed at the RV free wall near the tricuspid annulus in the apical four-chamber view, which is appropriate given the predominantly longitudinal contractile pattern of the right ventricle. By using pulsed-wave DTI, the peak velocity profiles are measured, in contrast to colour encoding

technique (colour DTI), which displays the average regional velocities. Pulsed-wave DTI provides a spectrum of velocities for each point in time, so as to choose the maximum velocity by measuring the outer border of the spectral envelope. Peak velocities may also be assessed from the mid- and apical portions of the RV free wall. The RV systolic and diastolic velocities are higher than LV velocities, and the RV velocities acquired by colour DTI technique are lower than pulsed-wave DTI velocities (16, 51). Also, there is an age-related change in the RV diastolic velocities (52-53). Pulsed-wave DTI is not dependent on endocardial border detection and geometric assumptions and has excellent temporal resolution. It is also highly reproducible with low intraobserver and interobserver variation (54). Limitations of DTI include dependence on the angle of insonation, as with any Doppler technique, and the translational myocardial motion - problems which may be minimized by obtaining the velocities along the long axis. Moreover, the rotation of the ventricles along the longitudinal axis is minimal and the cardiac apex is virtually fixed throughout the cardiac cycle (55). The systolic tricuspid annular velocity (Sm) reflects systolic longitudinal RV function. Previous studies have shown that the tricuspid Sm is a strong independent predictor of the RVEF, compared with RVEF determinations by magnetic resonance imaging and radionuclide ventriculography, and has also shown good correlation with RV fractional area change and TAPSE (56, 54, 57).

The tricuspid early (Em) and late (Am) diastolic annular velocities reflect diastolic RV function and can also be used to determine RV filling pressure (48, 58). The number of papers discussing RV diastolic function is far less than that discussing LV diastolic function and their results are sometimes contradictory, showing the need for further studies. One study identified the tricuspid Am, a reflection of the atrial contraction, as being correlated with the pulmonary artery systolic pressure (57), and another showed no difference in tricuspid Am between PE patients and age-matched controls or between PE patients with high and normal systolic pulmonary artery pressures (59). Reduction in tricuspid Em in patients with acute PE was seen in one study even with normal systolic RV pressures, normal tricuspid Sm, and normal RV filling pressures, suggesting the decrease in tricuspid Em to be an early sign of compromised RV function (59). Yet another study failed to report any change in tricuspid Em in PE patients compared with controls (52). Recent studies showed a significant decrease in tricuspid Em compared to some cardiac risk factors and in comparison with an increasing body mass index (BMI), thus reflecting worsening of RV diastolic function. The discrepancy between the different results may be due to different patient categories regarding severity of PE, age, and associated diseases.

Similar to assessments of the LV filling pressures, the ratio between tricuspid early diastolic inflow velocity determined by conventional Doppler (E) and corrected for the influence of RV relaxation by means of DTI-derived tricuspid Em (E/Em ratio) has been used as an index of RV filling pressures and shows good correlation with catheter measurements (60). Recent studies have reported a cut-off value for the E/Em ratio identifying patients with increased right atrial pressure (48, 58). Thus, the E/Em ratio has been suggested to be a useful index of RV filling pressure in different patients categories, especially when the inferior vena cava method cannot be used or with ongoing mechanical ventilation, but caution should be taken in patients early on after cardiac surgery (61).

Pulsed-wave DTI can also be used to determine the different cardiac time intervals, including isovolumic contraction time, isovolumic relaxation time and ejection time. These parameters can be used to calculate the myocardial performance index (MPI), another echocardiographic parameter predicting RV function. The MPI is a combinative index of the RV systolic and diastolic function and has been shown to correlate with radionuclide-derived RVEF (62). MPI has also shown to be useful in assessing patients with primary pulmonary hypertension, congenital heart disease and also for follow-up of patients with chronic thromboembolic pulmonary hypertension who undergo pulmonary endarterectomy (63-64). A previous study showed that, in conjunction with elevated right atrial pressure, the MPI can be falsely low in patients with myocardial infarction (65). Determination of the MPI by pulsed-wave DTI rather than by the more traditional blood-pool Doppler ultrasound technique enables simultaneous measurements of the time intervals from a single Doppler tracing during a single cardiac cycle compared to the two separate tracings, tricuspid inflow and pulmonary outflow, required for the blood-pool technique. The isovolumic relaxation time has been shown to be prolonged in patients with pulmonary arterial hypertension compared to patients with lung disease without pulmonary hypertension and healthy subjects (66). The isovolumic relaxation time was also directly related to pulmonary artery systolic pressure determined by echocardiography.

3D echocardiography is currently evolving with reports on several studies assessing the RV volumes and EF in comparison with CMR (67-68). RV volumes have been shown to correlate fairly well with CMR measurements, but they are 20-35% smaller than those obtained by CMR. This underestimation is more pronounced for more dilated ventricles and may be due to difficult border detection, especially in apical regions, and difficulty in image acquisition so as to include a complete data set for the right ventricle (69). The RV outflow tract may be difficult to include in the 3D dataset due to its very anterior location, often obscured by near-field artefacts. Contrarily, the RVEF shows good agreement with CMR measurements, suggesting that



volumetric measurement errors are consistent throughout the cardiac cycle. The reproducibility of 3D echocardiographic measurements showed an SD of the difference between repeated volume measurements of 10-20% of the mean measurement value (67-68). Also, the number of datasets that could be reliably analysed for RV volumes was reported to be between 50% and 80% (68-69). Although the off-line analysis is done with dedicated software, manual editing of detected borders is required. Thus, these disadvantages should be borne in mind, especially when considering serial measurements done by potentially different echocardiographers.

2D speckle tracking echocardiography (STE) is a new rapidly growing modality. It is reproducible and allows a complete analysis of radial and circumferential strain, twist, torsion, and rotation. Myocardial deformation is calculated from continuous frame-by-frame tracking of speckled myocardial patterns generated by irregularities in acoustic backscatter. Unlike tissue Doppler methods, STE is angle-independent but limited by poor echo windows. As with other techniques, the right ventricle's complex geometry, thinner walls, and increased trabeculation make it more difficult to obtain and interpret speckle information from the right ventricle than from the left ventricle. Most experience so far has been gathered by using regional and global RV peak systolic longitudinal strain, which compares well with DTI measurements. However, the effects of preload and afterload and the distribution of myocardial velocities, strain and strain rate still remain unclear (70).

### **1.2.2 Cardiac magnetic resonance imaging**

CMR is the most accurate of the various techniques currently available to quantify RV mass and volumes and is therefore considered to be the gold-standard technique for quantification of RV volumes in clinical practice. CMR is also the clinical reference technique for determining the RVEF due to the difficulties in measuring the RVEF echocardiographically, as discussed in the previous section. RV images can be acquired in the short-axis or axial direction. Axial orientation has been shown to result in better intraobserver and interobserver reproducibility than the short axis orientation (71). Cine sequences allow the visual assessment of the global and regional RV wall motion. Quantitative regional function analysis with strain-encoded imaging has been shown to be a reproducible approach for 3D deformation estimation. Despite its advantages, CMR is only reliable when adequately standardized (72). Its measuring accuracy depends on optimization of image acquisition and consistency in post-processing, which, especially for the right ventricle, requires extensive operator-dependent manual contouring. CMR provides information on tissue characteristics and can be used in the detection of

myocardial fibrosis or inflammation and enables early detection of regional fat accumulation. Owing to the limited availability and relatively high cost of CMR, its use is still limited.

### **1.2.3 Other methods for RV evaluation**

Radionuclide ventriculography can be used to determine the RVEF. Two different techniques, equilibrium-gated radionuclide ventriculography SPECT and first-pass radionuclide ventriculography, are available. The latter is based on a rapid injection of  $^{99m}\text{Tc}$  pertechnetate in a peripheral vein; which, after the passage of the radioactive substance, is followed through the central circulation by means of a low-energy high-resolution collimator on a gamma camera. Background corrected radionuclide time activity curves emanating from the RV chamber are used to calculate the RVEF from end-diastolic and end-systolic counts. Due to a limited number of heart beats, wall motion analysis is suboptimal. In the equilibrium-gated technique red blood cells are labelled with  $^{99m}\text{Tc}$  and changes in ventricular volume are followed over time. Both investigations are ECG-gated. The equilibrium technique allows estimations of the global and regional ventricular wall motion but requires a regular heart rate for representative results. Radionuclide ventriculography is an accurate and highly reproducible non-invasive method for determining RV function (73).

Cardiac computed tomography (CT) has made significant technological advances in recent years through reductions in radiation (prospective imaging, high-pitch 100kVp imaging and electrocardiographic dose modulation), improved temporal resolution with dual source scanning, increased supero-inferior coverage, improved injection protocols, and dual energy imaging. As a result, multidetector CT (MDCT) has broadened its field in cardiovascular diagnostics. Cine-MDCT is now possible due to improved temporal resolution. Using retrospective scanning, four dimensional functional data can be obtained or assessments of cardiac volumes and function. However, the radiation is significantly higher compared to the prospectively triggered scans, which limits its use considerably. In cases of suboptimal echocardiography or the presence of a pacemaker, cine-CT may be useful.

Cardiac catheterization is an invasive method and has partly lost its importance due to newer techniques such as echocardiography and CMR, but it is still useful, especially in patients with congenital heart disease and those with pulmonary hypertension. Right heart catheterization provides direct haemodynamic measurements and allows accurate assessments of pulmonary vascular resistance. Cardiac catheterization can be performed as a purely diagnostic procedure or as an interventional method. Right ventriculography is difficult to interpret and has been

superseded by echocardiography for the detection of RV dysfunction. By means of right heart catheterization, pressure-volume loops can be generated and quantify various determinants of RV function such as RV elastance and the rate of pressure development ( $dp/dt$  max), both being indexes of RV contractility, ventricular compliance, and stroke work.

### **1.3. Pulmonary embolism**

Task force guidelines from 2008 suggest a change in nomenclature in PE (74). Such previously used terms as “massive”, “submassive” and “non-massive” have been suggested to be replaced with the estimated level of the PE-related early death. Thus, current PE-classification includes a high-risk group (risk level > 15%), intermediate-risk group (risk level 3-15%), and a low-risk group (risk level < 1%). The intermediate-risk group and the low-risk group are also referred to as the non-high-risk group. The diagnostic approach and treatment are suggested to be in accordance with the risk groups.

Venous thromboembolism (VTE) is manifested most frequently by deep vein thrombosis (DVT) or by PE. PE is a common and potentially lethal condition with an age-related increase in incidence (75-76). Precise figures for the incidence of PE are not available due to non-specific clinical presentation and an unknown number of clinically silent emboli, leading to the conclusion that the actual disease frequency is underestimated. Also, the reported annual incidence rates of VTE differ between geographical regions, populations, diagnostic methods, and availability of autopsy data and has been estimated to range between 20 and 70 or 150 and 200 cases per 100 000 inhabitants, respectively, with about one-third of cases presenting as acute PE (77-79). Data from Malmö, Sweden, indicate a yearly incidence of PE of approximately 20/10 000 inhabitants (76). Estimates from Germany report a yearly PE mortality of up to 40 000 patients in that country (80). Also, about 10% of acute PE patients die after 1-3 months (81). If left untreated, approximately one-third of patients who survive an initial pulmonary embolism die of a subsequent embolic episode. Furthermore, a small fraction of surviving patients will later on develop chronic thromboembolic pulmonary hypertension (CTEPH) due to incompletely resolved thrombi. PE predisposing factors may be divided in permanent patient-related and more temporary situational factors and may also be classified as strong, moderate or weak. Idiopathic or unprovoked PE occurs in approximately 20% of cases (82). Recently, some inflammatory markers were found to be increased in idiopathic PE patients

compared to patients with secondary VTE, thus supporting the hypothesis that the former may share some predisposing factors with arterial thromboembolism (83).

**Table 1.** Predisposing factors for venous thromboembolism (74).

<b>Strong factors (OR &gt; 10)</b>	<b>Moderate factors (OR 2-9)</b>	<b>Weak factors (OR &lt; 2)</b>
Bone fracture (hip, leg)	Arthroscopic knee surgery	Bed rest >3 days
Hip or knee replacement	Central venous lines	Immobility due to sitting (e.g., prolonged car or plane travel)
Major general surgery	Heart or respiratory failure	Increasing age
Major trauma	Hormone replacement and oral contraceptive therapy	Laparoscopic surgery (e.g., cholecystectomy)
Spinal cord injury	Malignancy, chemotherapy	Obesity
	Immobility after stroke	Pregnancy (antepartum)
	Pregnancy (peripartum) - Lactation	Chronic venous insufficiency, varicose veins
	Previous VTE	
	Thrombophilia	

OR – odds ratio for different predisposing factors

The diagnosis is often missed because patients with pulmonary embolism present with non-specific signs and symptoms. The most common symptoms of pulmonary embolism in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study were dyspnoea (73%), pleuritic chest pain (66%), cough (37%), and haemoptysis (13%). However, patients with pulmonary embolism may present with atypical symptoms. The most common signs in the PIOPED II study were tachypnoea- > 20/min (70%), rales (51%), and tachycardia - > 100/min (30%), and the most common risk factor assessed in PE patients was immobilization, usually because of surgery. Fever may be present, but high temperatures are more frequently from other

sources than PE. In several series, dyspnoea, tachypnoea, or chest pain were present in more than 90% of PE patients (84).

Clinical prediction rules are used to classify suspected PE patients in categories of pre-test probability corresponding to increasing prevalences of PE. The Wells score and the revised Geneva rule are both extensively validated pre-test probability scores (85-86). Both scores are composed of easily gathered variables of pre-disposing factors, symptoms, and clinical signs resulting in 2 or 3 levels of clinical probability depending on the score chosen. Interobserver reproducibility for the Wells score has been found to be variable. The proportion of PE patients in the different probability categories is the same for both scores. The two-category Wells score, combined with the moderately sensitive D-dimer assay, is widely used to rule out PE in patients with a negative D-dimer and categorized as PE being unlikely, thus reducing the need for additional diagnostic testing in these patients. Patients with a low or moderate pre-test probability of PE and a negative D-dimer in a highly sensitive assay can be safely excluded regarding PE, as can those with a moderately sensitive D-dimer assay in combination with a low clinical probability. D-dimer, a degradation product produced by plasmin-mediated proteases of cross-linked fibrin, is elevated in plasma in VTE due to the simultaneous activation of coagulation and fibrinolysis. Therefore, its negative predictive value in PE is high. The specificity of D-dimer, however, decreases with age, and may also be elevated in conjunction with concomitant inflammatory conditions and other diseases. Therefore, D-dimer is of limited value in patients who are over 80 years old, hospitalized, or who have cancer, and also during pregnancy (74).

The choice of diagnostic imaging method in PE depends largely on the 24-hour availability of the different methods, and on local traditions and expertise. Pulmonary angiography has been the gold standard for the diagnosis of PE, but it is now rarely used due to newer techniques offering similar or superior information, such as CT angiography, which also has the advantage of being non-invasive. With direct angiography, thrombi as small as 1 or 2 mm within the subsegmental arteries can be seen; however, there is substantial interobserver variability at that level (87). Pulmonary angiography provides haemodynamic data, and treatment of the detected PE is possible in the same clinical setting, but it is associated with both fatal and non-fatal complications (88). Multi-detector CT (MDCT) angiography with high spatial and temporal resolution and quality of arterial opacification allows adequate visualization up to at least the segmental level. Different sensitivity and specificity values have been reported (89-90). In the PIOPED II study patients with a low or intermediate PE probability and a negative CT had high negative predictive values for PE (96% and 89%, respectively), but only 60% with a high pre-

test probability. Also, patients with an intermediate or high PE probability and a positive CT had positive predictive values of 92-96%, but only 58% in patients with low pre-test probability. Thus, negative MDCT may be used to exclude PE in non-high-clinical probability patients, but in high-probability patients further testing is needed. Also, since the positive predictive value is low in patients with a low clinical probability, positive MDCT should be verified by additional tests (89).

Ventilation-perfusion scintigraphy (V/Q scan) is a non-invasive, well-established method and has been validated in several clinical trials with low event rates (91). Thus, a normal perfusion scan is safe for excluding PE. Additionally, the V/Q scan has been proved safe with few allergic reactions. Traditionally, planar perfusion and ventilation images in at least six projections are used. For increased specificity, a ventilation scan is performed, and yields a specific perfusion-ventilation mismatch pattern with normal ventilation in hypoperfused segments. Due to a relatively high frequency of non-diagnostic V/Q scans with planar imaging, leading to additional diagnostic testing, data acquisition in the tomographic mode has recently been introduced. Using single photon emission computed tomography (SPECT), diagnostic accuracy is increased with fewer non-diagnostic tests. In recent studies, the negative predictive value for V/Q SPECT was 97-99%, sensitivity 96-99% and specificity 91-98% for PE diagnoses, proving the high accuracy of the method. Rates of non-diagnostic findings were 1 to 3% (92-93).

2008 guidelines recommend the stratification of patients based entirely on the clinical evaluation, namely the presence of shock or systemic hypotension, defined as a systolic blood pressure  $< 90$  mmHg or its fall by  $\geq 40$  mmHg compared to the usual level for at least 15 minutes and without an apparent alternative cause. Thus, different diagnostic algorithms are suggested for high-risk and non-high-risk patients.

In high-risk PE-suspected patients, a straightforward strategy is proposed to confirm or exclude haemodynamically significant PE and to allow differential diagnostics without time delay. CT angiography is given the first-choice status, with bedside echocardiography as an alternative in cases of critically ill, unstable patients.

In non-high-risk PE-suspected patients the strategy is to identify those who, according to Wells or Geneva scores, are classified at low or moderate pre-test probability. In these patients, a negative D-dimer assay may safely exclude PE as discussed earlier. Patients with a high pre-test probability or positive D-dimer assay require a diagnostic imaging test. The preference between available methods in guidelines is given to MDCT angiography due to a higher proportion of inconclusive results by V/Q scintigraphy (74), and the V/Q scan is suggested to be

a valid option for patients with contraindication to CT, such as allergy to iodine contrast dye or renal failure. The prognostic assessment should be carried out simultaneously with the PE diagnosis in order to allow a proper choice of therapy and risk stratification. For this purpose, non-high-risk patients are further divided into an intermediate-risk group and a low-risk group, the former showing signs of RV dysfunction and/or injury and the latter lacking them.

In this context echocardiography is considered to be a key test for predicting the short-term outcome. A recent meta-analysis including five prospective studies of haemodynamically stable PE patients demonstrated a 44% occurrence of RV dysfunction and short-term mortalities of 10% and 3%, respectively, for patients with and without RV dysfunction. The risk of death due to PE was shown to be elevated by a factor of 2.5 in patients with RV dysfunction, which also had a negative predictive value for all-cause mortality of 97% (94). A more than two-fold increased risk for PE-related mortality in conjunction with signs of RV dysfunction was found in another meta-analysis (95).

While signs of RV dysfunction are important in risk stratification, there are no universal cut-off levels at present and no therapeutic recommendations are available solely on the basis of RV dysfunction in otherwise non-high-risk patients. Since about 25% of these patients will have a complicated clinical course, they should be closely monitored to enable early rescue therapy (96). Thus, routine thrombolysis is not recommended, but it may be considered in selected patients. An ongoing randomized trial is assessing the potential benefit of thrombolysis in PE patients with echocardiographic signs of RV overload.

When elevated, markers of cardiac injury, troponin T or I, are associated with an intermediate risk in short-term mortality in acute PE (97). Also, normal troponin levels indicate a good prognosis in the acute stage. The prognostic assessment is currently limited due to a lack of universally accepted criteria.

Several studies have shown a low in-hospital PE-related mortality of < 1% in patients with normal echocardiographic findings (98-99). The outcome for these patients may also be influenced by co-morbidities and their general condition. In this regard, the pulmonary embolism severity index (PESI) may be helpful to accurately identify patients with a low risk for overall mortality in the first 30 days after a PE diagnosis (100). This would allow early discharge and treatment in an out-patient setting.

## **1.4. Right ventricle in pulmonary embolism**

Pulmonary emboli usually arise from the thrombi originating in the deep venous system of the lower extremities. The haemodynamic consequences are dependent on the size and number of the emboli and on coexisting cardiovascular diseases. Large thrombi can lodge at the bifurcation of the main pulmonary artery or the lobar branches and cause haemodynamic compromise at a level of approximately over 30-50% of occlusion of the pulmonary bed (101). A relatively moderate PE can prove to be fatal in a patient with cardiovascular disease. The series of events in PE begins with an acute increase in pulmonary vascular resistance brought on mainly by the mechanical obstruction by emboli and, to some extent, by pulmonary vasoconstriction (102-103). An increase in pulmonary vascular resistance leads to pulmonary hypertension and to an acute rise in RV afterload. The force opposing the shortening of muscle fibres i.e. afterload, is a major determinant of myocardial performance. The concept of afterload reflects the interrelationship between ventricular wall thickness, chamber dimensions and chamber pressure, all of which directly affect the response to afterload at the myocardial level. The thin-walled right ventricle has been shown to be highly sensitive to afterload changes (78). An increase in RV wall tension may lead to systolic RV dysfunction, RV dilatation with secondary tricuspid regurgitation, and elevated RV end-diastolic pressure and volume. Dilatation of the right ventricle is a compensatory mechanism that allows it to maintain the stroke volume despite a decreased ejection fraction (104). The combination of impaired RV systolic function and tricuspid regurgitation decreases RV output, which, combined with decreased LV compliance, reduces LV filling and stroke volume. Inotropic and chronotropic stimulation and the Frank-Starling mechanism result in increased pulmonary artery pressure, leading to the restoration of resting pulmonary flow, LV filling, cardiac output, and systemic perfusion (105). However, the right ventricle is not expected to be able to generate mean pulmonary artery pressures exceeding 40 mmHg (101). These compensatory mechanisms are particularly important since a decline in cardiac output may further impair cardiac function by decreasing RV coronary perfusion and precipitating myocardial ischaemia.

The two ventricles are composed of layers of tightly bound myocardial fibres that encircle both ventricles (1,5). Three major structures couple the right and left heart: the pulmonary circulation, the interventricular septum and the pericardium. When an acute increase in afterload affects one ventricle independently of the collateral ventricle in an intact circulation, as in acute PE, the resulting effects on the diastolic pressure-volume relationship of the contralateral ventricle are dependent on pericardial restraint in addition to loading conditions produced by



shifting of the septum and peripheral circulatory impedance. The normal pericardium can accommodate about a 20% acute increase in cardiac volume before pericardial constraint leads to an increase in the ventricular filling pressure. Therefore, acute distension of the right ventricle during diastole leads to a shift in the LV pressure-volume curve, reflecting decreased LV compliance (25, 28). These changes seem to be the result of a reversal of the transseptal pressure gradient and a marked leftward shift of the interventricular septum which alters the shape of the left ventricle (106). With an intact pericardium, an acute augmentation of the RV volume leads to a decrease in LV volume because of the restricting influence of the pericardium which prevents the total heart volume from increasing.

After an acute embolic episode, a secondary haemodynamic destabilization may occur as a result of recurrent emboli and/or deterioration of RV function, usually within 24–48 hours from the initial event. The compensatory mechanisms which increase sympathetic tone may also fail to maintain RV function in the long term even in the absence of recurrent embolic events (107). Pre-existing cardiovascular disease may also influence the efficacy of compensatory mechanisms (82). Some previous studies have identified age > 70 years and a systolic pulmonary artery pressure > 50 mmHg as risk factors for developing chronic pulmonary hypertension (99). The level to which pulmonary vascular resistance rises determines the severity of the haemodynamic alterations induced by PE. Large or multiple emboli might abruptly increase the level of afterload to an extent which leads to sudden death or syncope or systemic hypotension due to acute RV failure. In patients with any pre-existing cardiopulmonary disease, even relatively small to moderate emboli may cause RV dysfunction and thus affect the patient's prognosis. It is mandatory to determine the RV function in PE patients at an early stage, even in non-high-risk patients, as it is a decisive factor for risk evaluation and therefore the choice of treatment, level of monitoring and short-term as well as long-term prognosis.

## 2 AIMS OF THE THESIS

The overall aim of this thesis was to evaluate RV function in patients with acute PE and its relationship with pulmonary perfusion as well as with clinical pre-test probability scores, by using echocardiographic techniques.

In different papers the specific aims were:

**Study I:** To evaluate systolic and diastolic RV function by means of the M-mode derived tricuspid annular plane systolic and diastolic excursion in patients with acute PE and changes over time.

**Study II:** To determine the feasibility of using pulsed-wave Doppler tissue imaging to detect RV dysfunction and to estimate RV filling pressure in acute PE, and also to assess change in the values over time in relation to the clinical status.

**Study III:** To assess the correlation of D-dimer, the Wells score, and the PESI with echocardiographic RV parameters and to determine the specific cut-off value of D-dimer and its association with RV function in acute PE. Also to evaluate any possible additional value of the PESI to that of D-dimer.

**Study IV:** To assess the relationship of the extent of the pulmonary perfusion with echocardiographic parameters, and to determine whether a certain limit of perfusion loss would be associated with RV dysfunction. And to evaluate the possible value of a new method for expressing perfusion inhomogeneity.

### 3 PATIENTS AND METHODS

#### 3.1 Patients (I-IV)

##### **Exclusion criteria for studies I-IV**

- 1) Coronary artery bypass graft or other thoracic surgery
- 2) Pace-maker
- 3) Left bundle branch block, LBBB
- 4) Atrial fibrillation
- 5)  $\geq 2$  previous PEs or deep-vein thromboses
- 6) Unstable haemodynamics
- 7) Unsatisfactory quality of the echocardiogram

**Study I:** This study was conducted at the Karolinska University Hospital Solna and Södersjukhuset, Stockholm, Sweden. One hundred and forty-six patients were initially investigated at the emergency departments with clinical suspicion of PE. Forty patients with a confirmed diagnosis of PE were included in the present study. The mean age of the patients was 58 years (range 29-80), and there were 19 females and 21 males. The patients were scored for symptoms related to PE and investigated with echocardiography on admission and 3 months later.

**Studies II and III:** Thirty-four patients with confirmed PE were included in these studies. Patients were recruited from the emergency departments of the Karolinska University Hospital Solna and Södersjukhuset, Stockholm, Sweden. The mean age of the patients was 65 years (range 29-80).

**Study IV:** Fifteen patients, 4 females, with confirmed PE were included in this study. All patients were recruited at the Karolinska University Hospital Solna. The mean age of the patients was 63 years (range 40-78). All patients were studied by lung scintigraphy and by echocardiography on admission. The patients were also compared with a scintigraphic clinic standard.

**Study I, II and IV:** Twenty-three age- and sex-matched controls were investigated by echocardiography according to the same protocol as for the patients.

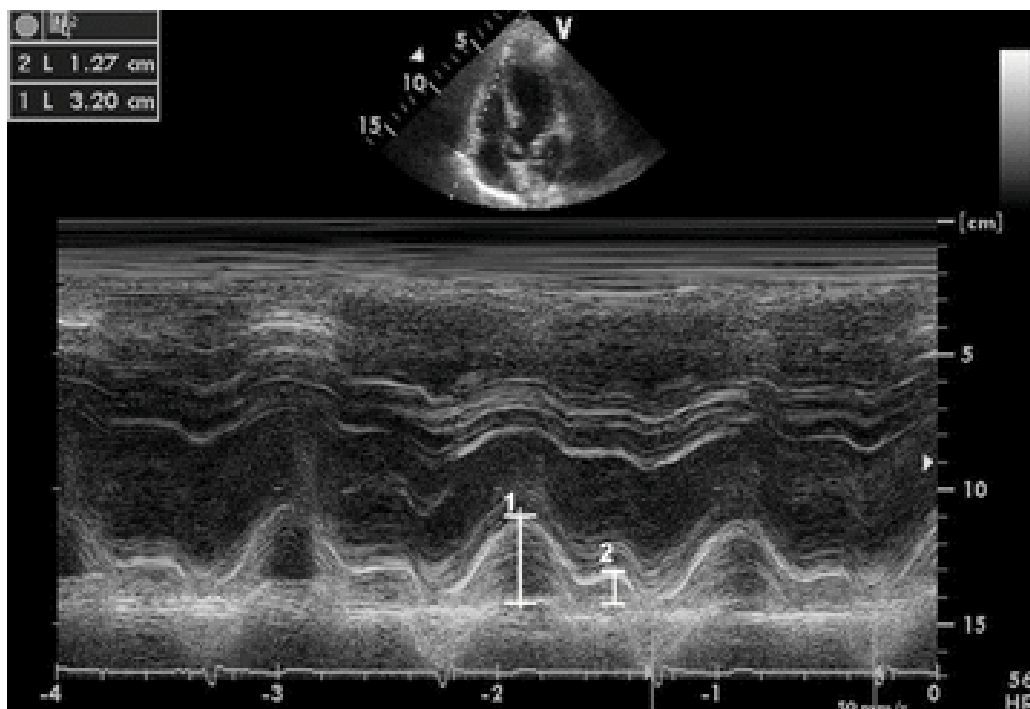
## **3.2 Methods**

### **3.2.1 Echocardiography (Paper I)**

Echocardiography was performed using the same technique at both hospitals. All studies were done within 24 hours from the patient's admission and after three months. Commercially available echocardiographic equipment was used (Sequoia, Siemens, Mountain View, CA, USA or Vingmed System V, GE, Horten, Norway). The echocardiographic variables analysed were:

- 1) The different cardiac dimensions and left ventricular ejection fraction according to the recommendations of the American Society of Echocardiography.
- 2) The RV end-diastolic dimension from an apical 4-chamber view orthogonal to the long axis, one-third of the distance from the base.
- 3) The tricuspid annular plane systolic and diastolic excursion from the apical 4-chamber view. The M-mode cursor was placed at the junction of the RV free wall and the tricuspid valve in such a way that the tricuspid annulus moved along the M-mode line and the maximal longitudinal shortening and relaxation of the RV free wall was recorded. The amplitude of the excursion of the tricuspid annulus from the base towards the apex in systole was defined as TAPSE. The percentage of tricuspid annular plane excursion during the right atrial contraction to the total tricuspid annular plane diastolic excursion was defined as atrial/total TAPDE and used as an indicator of diastolic RV function. All the RV parameters were based on five consecutive good-quality beats.
- 4) The longitudinal RV fractional shortening from the apical four-chamber view, using the ratio of TAPSE to RV length (measured from the outer part of the apex to the tricuspid annulus at diastole), was measured.
- 5) The mitral annular excursion at the septal and lateral mitral walls of the left ventricle was also calculated.
- 6) A qualitative visual segmental wall motion analysis of the right ventricle and RVEF from the 4-chamber view was made.
- 7) McConnell's sign was considered positive in the presence of an abnormal motion of the mid-free wall of the right ventricle.
- 8) The global RVEF was defined as normal or mildly, moderately or severely depressed.
- 9) The degree of tricuspid regurgitation (TR) was assessed qualitatively from colour-flow Doppler recordings and classified as absent, physiological, mild, moderate, or severe.

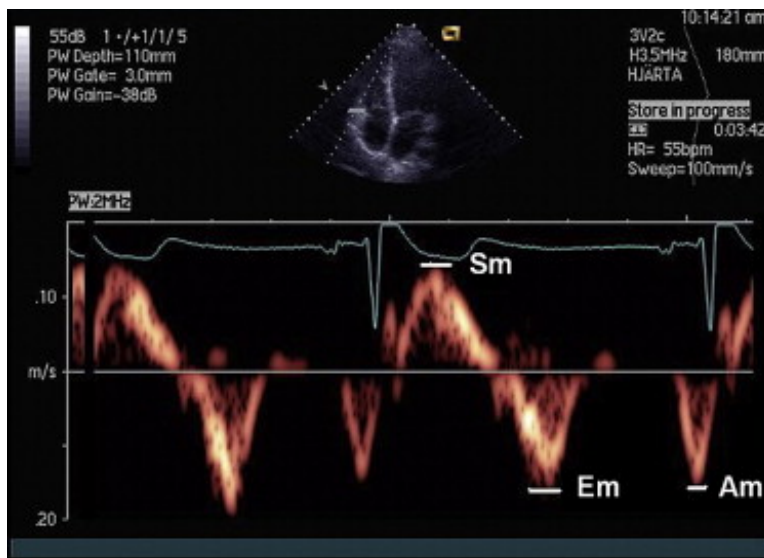
- 10) The systolic RV pressure was calculated from the summation of the estimated right atrial pressure (RAP) and the peak difference in pressure between the right atrium and ventricle ( $\Delta P$ ). The  $\Delta P$  was measured by applying the simplified Bernoulli equation ( $\Delta p = 4 \times V^2$ ) to the maximum velocity of the TR Doppler signal. The value for the RAP was estimated by measuring the end-expiratory diameter of the inferior vena cava and the change in the diameter during inspiration. If the diameter of the inferior vena cava was less than 2.5 cm and the inspiratory collapse was greater than 50%, the estimated right atrial pressure was estimated to be 5 mmHg and if the inspiratory collapse was less than 50%, the estimated right atrial pressure was 10 mmHg. If the inferior vena cava diameter was above 2.5 cm and there was an inspiratory collapse of less than 50%, the right atrial pressure was estimated to be 15 mmHg and if there was no inspiratory change in the caval diameter, the right atrial pressure was estimated to be 20 mmHg. A normal RV pressure was defined as  $< 40$  mmHg.
- 11) A visual assessment of the interventricular septal movement from the parasternal short axis view and from the apical 4ch-view was made and determined to be abnormal if a flattened septum or paradoxical septal motion was present.



**Figure 2.** M-mode recording of the total (1) and atrial (2) tricuspid annular motion.

### 3.2.2 Echocardiography (Paper II, III and IV)

Echocardiography was performed as in study I. In addition, myocardial velocities using pulsed-wave DTI were obtained at the RV free wall and at the basal septal and lateral segments of the left ventricle. The peak annular tricuspid and mitral systolic (Sm) and early (Em) and late (Am) diastolic velocities were measured from the myocardial velocity profiles. The tricuspid Sm was measured with exclusion of the velocities recorded during isovolumic contraction. The resulting velocities were recorded for 5 consecutive cardiac cycles. The pulsed wave cursor was aligned in such a way that the annulus moved along the sample volume line, always keeping the angle of insonation at less than 20 degrees. The sample volume was repositioned in the same location when required. Recordings were made whenever possible with patients holding their breath at the end expiration, otherwise during as shallow respiration as possible. A small sample volume size was used, adjusted proportionally to the annular motion. Filters were set to exclude high-frequency signals and gains were minimized to allow a clear tissue signal with minimal background noise. There was no offline manipulation of the obtained curves. The isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), and ejection time (ET) were measured from the RV free wall near the tricuspid annulus for calculation of the MPI according to the method,  $(IVCT + IVRT)/ET$ . Non-invasive RAP was assessed by using the ratio between the tricuspid early diastolic inflow velocity and the tricuspid annular early diastolic velocity (tricuspid E/Em). The RAP was also derived from the inferior vena cava as in study I. Non-invasive pulmonary vascular resistance (PVR) was calculated in Wood units (WUs) using the ratio of the tricuspid regurgitation velocity (TRV) and RV outflow tract time-velocity integral (TVI<sub>rvot</sub>) multiplied by 10, i.e.  $10 \times TRV/TVI_{rvot}$ .



**Figure 3.** Recording of peak systolic (Sm), early (Em) and late (Am) diastolic velocities of the RV free wall near the tricuspid annulus in a subject.

### **3.2.3 Pulmonary arteriography (Paper II)**

Invasive mean right atrial pressures were obtained in 10 patients undergoing pulmonary angiography (PA) prior to contrast injection. The PA was performed using Seldinger technique via the common femoral vein and pig-tail catheters (Cook, Inc., IN, USA) connected to an electrically calibrated fluid-filled transducer (Navilyst Medical, Inc. MA, USA) positioned at the mid-chest level of the patient with the zero level at the mid-axillary line. A chest x-ray was used to verify the catheter position. Pressure measurements were acquired at end-expiration and represent the average of five cardiac cycles. All patients had ECG-monitoring during the procedure. The right atrial pressure waves were determined by two independent observers.

### **3.2.4 D-dimer assay (Paper III)**

Blood samples were obtained upon arrival at the hospital and the citrate plasma was frozen and stored at  $-70^{\circ}\text{C}$  at the local coagulation unit. For the D-dimer test a semiquantitative rapid latex agglutination procedure was used (Tinaquant®, Roche). D-dimer concentrations were analysed and the cut-off level was set at  $< 0.5 \text{ mg/L}$ , according to the recommendation of the hospital laboratories and values  $< 0.5 \text{ mg/L}$  were reported as  $0.49 \text{ mg/L}$ .

### **3.2.5 PESI and Wells score (Paper III)**

All patients were classified by the pulmonary embolism severity index (PESI) and by the Wells pre-test probability score. Patients were divided into two groups (I-II and III-V) according to the PESI class to correlate with the clinical significance of the class. Two of the PESI predictors, heart failure and altered mental status, as originally described by Aujesky et al. (108), were not included in the risk score in this study. None of the patients showed signs of disorientation, lethargy, stupor, or coma; however, since the predictor altered mental status was not in the original study protocol, it was not included. Likewise, the PESI predictor heart failure was not included because RV dysfunction was one of the key parameters in study III. Moreover, all the patients had normal left ventricular systolic function by echocardiography. Other parameters were included, and scored points between +10 and +60, respectively, and the age in years were added. All clinical data were entered in the study protocol on admission. All seven variables in the Wells score were included. Since the inclusion criteria in the study were “signs or symptoms of PE”, all patients were considered to comply with the Wells criterion,

“pulmonary embolism as likely as or more likely than an alternative diagnosis”, thus scoring at least three points. The attending physician had no knowledge of the D-dimer levels or the results of the radiological or echocardiographic investigations prior to scoring the patients.

**Table 2.** PESI score (108).

	Points
Age, per year	Age, in yrs
Male sex	+ 10
Cancer	+ 30
Heart failure	+ 10
Chronic lung disease	+ 10
Pulse $\geq$ 110/min	+ 20
Systolic blood pressure < 100 mm Hg	+ 30
Respiratory rate $\geq$ 30/min	+ 20
Temperature < 36°C	+ 20
Altered mental status*	+ 60
Arterial oxygen saturation < 90% °	+ 20

\* Defined as disorientation, lethargy, stupor, or coma.

° With and without the administration of supplemental oxygen.

Points assignments correspond with the following risk classes:  $\leq$  65 class I, very low risk; 66-85 class II, low risk; 86-105 class III, intermediate risk; 106-125 class IV, high risk; > 125 class V, very high risk.

**Table 3.** Wells score for PE (86).

	Score
An alternative diagnosis is less likely than PE	3.0
Clinical signs and symptoms of DVT	3.0
Heart rate > 100 beats per minute	1.5
Previous VTE	1.5
Immobilization or surgery within 4 weeks	1.5
Hemoptysis	1.0
Malignancy	1.0

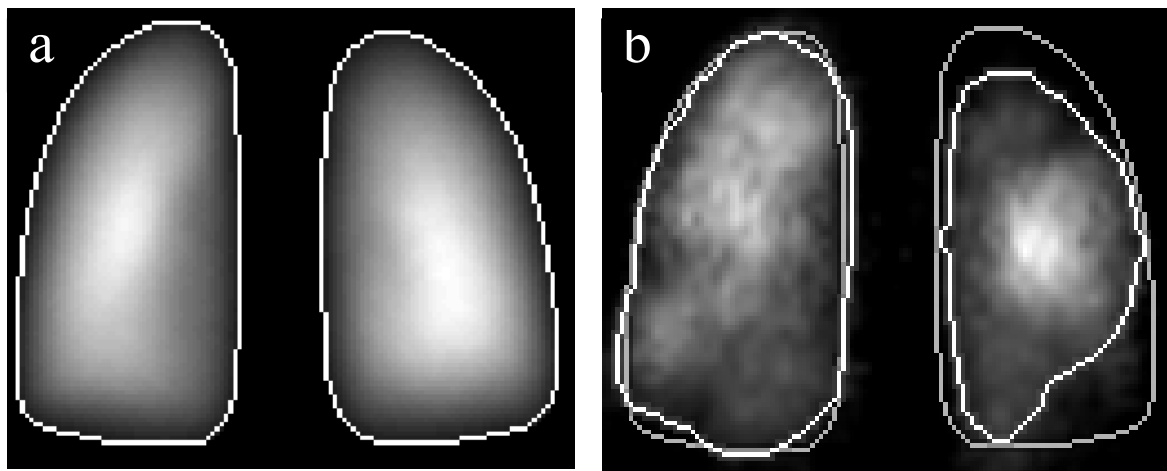
Clinical probability (3 levels); low 0-1 point, intermediate 2-6 points, high  $\geq$  7 points

Clinical probability (2 levels); PE unlikely 0-4 points, PE likely > 4 points



### 3.2.6 Lung scintigraphy (Paper IV)

Perfusion lung scintigraphy was performed following the intravenous injection of approximately 70MBq  $^{99m}\text{Tc}$  macro-aggregated albumin (Solco Nuclear, Switzerland) with the subject supine. All examinations were performed with a parallel-hole, low energy collimator on a gamma camera (General Electric 400 AT, USA). All scintigraphies were analysed on admission with respect to the extent of perfusion defects compared with a reference image. Patients were divided into two groups for further analysis using echocardiographic parameters: patients with a loss of perfused lung area  $< 10\%$ , and patients with a loss of perfused lung area  $\geq 10\%$  compared with reference. Only dorsal planar images were used in the analysis. Ventilation scintigraphy was not performed. The degree of perfusion inhomogeneity was analysed by the maximal count intensity observed in the lung scan. A reference image was created retrospectively from patients with suspected PE referred for lung scintigraphy and in whom the lung contours were deemed to be anatomically normal and with a distribution considered to be homogeneous by two experienced observers.



**Figure 4.** Lung perfusion images - dorsal projection. a) Mean distribution calculated from control subjects (reference image). The white contour indicates the perfused area b) Patient image; the white contour indicates the perfused area. The grey contour represents the reference area.

## **4. ETHICAL CONSIDERATIONS**

All studies were approved by the local Ethical Committee of Karolinska Institutet, Stockholm, Sweden. The informed consent of all patients was obtained.

## 5. MAIN RESULTS

### 5.1. PAPER I

The systolic and diastolic blood pressures were  $138 \pm 17$  mmHg and  $82 \pm 11$  mmHg, respectively. The duration of symptoms at inclusion ranged from 3 hours to 12 days with an average time of 2.9 days and a median time of 46 hours. No correlation between duration of symptoms and the RV systolic pressure or the TAPSE and TAPDE was found. Two patients had moderate, 15 patients mild, and 23 patients physiological tricuspid regurgitation.

**Table 4.** PE patients and healthy subjects, day 1.

	Healthy subjects	Patients
Number	23	40
Age (years)	$57 \pm 11$	$58 \pm 15$
Heart rate (beats/min)	$65 \pm 8$	$81 \pm 20^{***}$
LV end-diastolic dimension (mm)	$47 \pm 4$	$45 \pm 7$
LV ejection fraction (%)	$62 \pm 5$	$58 \pm 5^{**}$
Transmitral E/A ratio	$1.2 \pm 0.3$	$0.9 \pm 0.2^{***}$
Transtricuspid E/A ratio	$1.3 \pm 0.3$	$0.9 \pm 0.2^{***}$
RV end-diastolic dimension (mm)	$24 \pm 3$	$34 \pm 5^{***}$
Tricuspid regurgitation velocity (m/s)	---	$2.9 \pm 0.5$
RV systolic pressure (mmHg)	---	$44 \pm 15$
TAPSE (mm)	$26 \pm 4$	$19 \pm 5^{***}$
TAPDE during atrial contraction (mm)	$10 \pm 2$	$9 \pm 3$
Atrial/total diastolic excursion (%)	$38 \pm 7$	$47 \pm 13^{***}$
Systolic septal MAM (mm)	$14.2 \pm 2.3$	$11.7 \pm 2.3^{***}$
Systolic lateral MAM (mm)	$15.0 \pm 3.2$	$13.0 \pm 2.9^{**}$

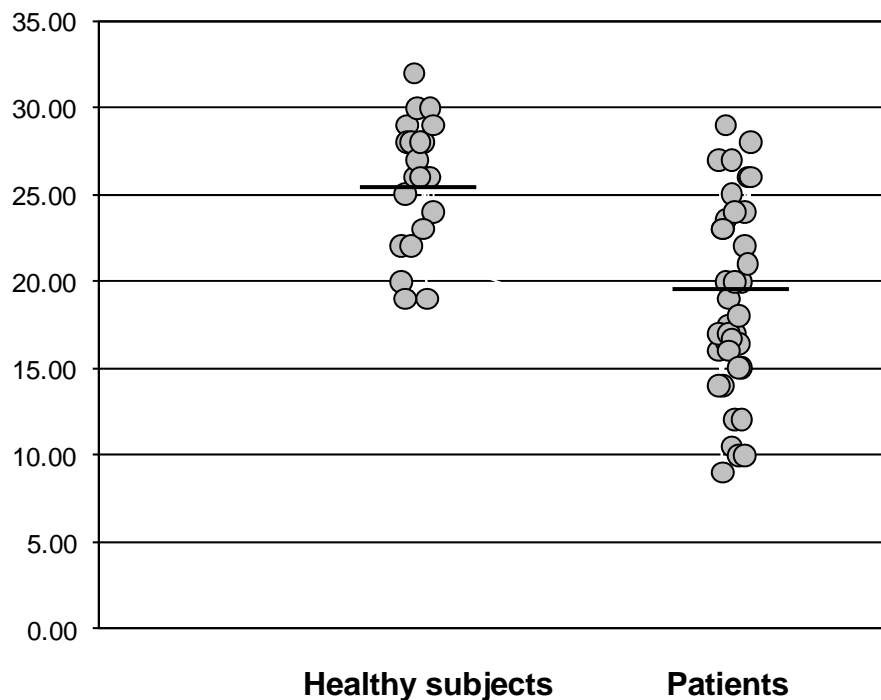
\*\* =  $P < 0.01$  and \*\*\* =  $P < 0.001$

**Table 5.** PE patients divided according to their RV systolic pressure.

	RV systolic pressure	
	(< 40 mmHg )	(≥ 40 mmHg )
Number	24	16
RV systolic pressure (mmHg)	32 ± 4	55 ± 12
RV end-diastolic dimension (mm)	34 ± 6	34 ± 3
TAPSE (mm)	20.5 ± 5	16.6 ± 5 *
Systolic septal MAM (mm)	11.7 ± 2.6	11.6 ± 1.9
Systolic lateral MAM (mm)	13.2 ± 3.1	12.8 ± 2.5
Abnormal septal motion (n)	5	11

\* =  $P < 0.05$ .

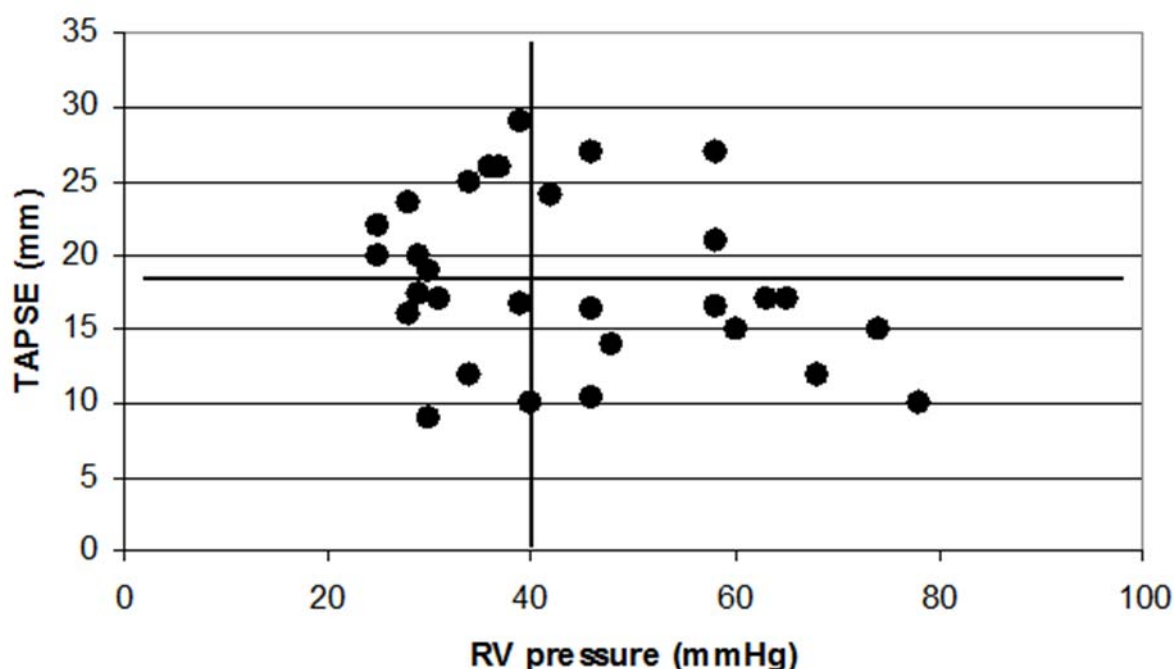
A normal TAPSE ( $\geq 18$  mm) was recorded in 51% of the patients and in all healthy subjects (Figure 5). TAPSE improved at follow-up compared to acute stage ( $19 \pm 5$  mm vs  $21 \pm 4$  mm,  $P < 0.05$ ), but was still lower than in healthy subjects ( $21 \pm 4$  mm vs  $26 \pm 4$  mm,  $P < 0.001$ ). Atrial contribution to total TAPDE normalised at follow-up compared to acute stage ( $47 \pm 13\%$  vs.  $40 \pm 10$ ,  $P < 0.05$ ), and compared to healthy subjects ( $40 \pm 10\%$  vs  $38 \pm 7\%$ , ns). There was a weak but significant correlation negative correlation between the increase RV systolic pressure and TAPSE ( $r = -0.27$ ,  $P < 0.01$ ).



**Figure 5.** Values of tricuspid annular plane systolic excursion for individual patients and healthy subjects. Lines represent mean values.

Nine (38%) of the patients with a normal systolic pressure and 12 (75%) of patients with an increased systolic pressure had decreased TAPSE (Figure 6). Eleven patients (69%) had abnormal septal movement in the group with increased RV systolic pressure compared to five patients (21%) in the group with normal pressure.

The reproducibility for analysing the tricuspid annular excursion was high (variation  $4\pm 3\%$  and the absolute value for an individual subject was  $\leq 1$  mm).



**Figure 6.** Distribution of RV systolic pressure and tricuspid annular plane systolic excursion (TAPSE) in patients in the acute stage. Some patients have identical values and cannot be distinguished separately in this figure.

## 5.2. PAPER II

The mean age of the patients was  $65 \pm 13$  years. The systolic and diastolic blood pressures were  $145 \pm 16$  mmHg and  $89 \pm 14$  mmHg, respectively. The mean transcutaneous oxygen saturation for the patient group was  $94 \pm 3\%$ . There were no in-hospital deaths in our study. One patient died during follow-up. At the 3-month follow-up, most of the patients were totally recovered clinically and only two patients reported mild dyspnoea. Heart rate was decreased at follow-up ( $77 \pm 16$  vs  $70 \pm 13$  beats/min,  $P < 0.01$ ).

**Table 6.** Comparison between patients on day 1 and healthy controls.

	Healthy	Patients
Heart rate (beats/min)	$65 \pm 8$	$77 \pm 16^{**}$
Tricuspid annular velocity (cm/s)		
Systolic (Sm)	$14.8 \pm 1.8$	$12.9 \pm 3.1^*$
Early diastolic (Em)	$15.3 \pm 3.6$	$11.9 \pm 3.6^{**}$
Late diastolic (Am)	$16.4 \pm 3.6$	$17.8 \pm 5.1$
Tricuspid E/Em	$3.5 \pm 0.7$	$4.5 \pm 2.0^*$
TAPSE (mm)	$26 \pm 4$	$19 \pm 5^{***}$
RV end-diastolic dimension (mm)	$24 \pm 3$	$34 \pm 5^{***}$
Mitral annular velocity (cm/s)		
Septal systolic (Sm)	$9.0 \pm 1.5$	$8.6 \pm 2.5$
Septal early diastolic (Em)	$12.0 \pm 2.5$	$9.2 \pm 3^{***}$
Lateral systolic (Sm)	$10.4 \pm 1.8$	$10.7 \pm 3.1$
Lateral early diastolic (Em)	$15.0 \pm 2.8$	$12.0 \pm 4.5^{***}$
LV ejection fraction (%)	$62 \pm 5$	$58 \pm 5^{**}$
Transmitral E/A ratio	$1.2 \pm 0.3$	$0.9 \pm 0.2^{***}$
LV end-diastolic dimension (mm)	$47 \pm 4$	$45 \pm 7$

\* =  $P < 0.05$ , \*\* =  $P < 0.01$ , \*\*\* =  $P < 0.001$

The intraobserver variabilities in tricuspid annular Sm, Em and Am were low:  $5.2 \pm 2.1\%$ ,  $5.3 \pm 3.7$  and  $5.8 \pm 1.0\%$ , respectively. Similar low results were also obtained on assessing the interobserver variabilities:  $6.3 \pm 2.1\%$ ,  $5.0 \pm 0.8\%$ , and  $2.0 \pm 1.6\%$ , respectively. There was no correlation between tricuspid Am and RV filling pressure. The MPI for the whole patient group was  $0.64 \pm 0.29$ . Patients with increased systolic RV pressure had a higher MPI than patients with normal systolic RV pressure ( $0.76 \pm 0.31$  vs.  $0.40 \pm 0.16$ ,  $P < 0.001$ ). Patients with normal systolic RV pressure had a lower tricuspid Em compared to healthy controls ( $12.8 \pm 3.9$

vs  $15.3 \pm 3.6$ ,  $P < 0.05$ ) but did not differ regarding tricuspid Sm or tricuspid Am (Sm  $13.7 \pm 3.1$  vs  $14.8 \pm 1.8$  cm/s and Am  $17.2 \pm 4.9$  vs.  $16.4 \pm 3.6$  cm/s,  $P = \text{ns}$  for both).

**Table 7.** Tricuspid annular velocities in patients with increased or normal right ventricular (RV) pressure during inclusion and at follow-up

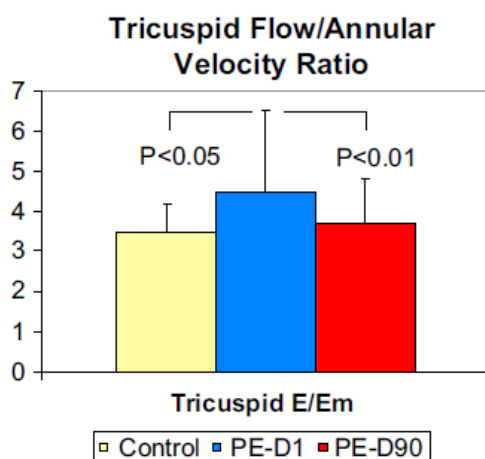
	<u>RV systolic pressure</u>			
	(< 40 mmHg )		( $\geq$ 40 mmHg )	
	Day 1	Day 90	Day 1	Day 90
Tricuspid annular velocity (TAV)				
Systolic, Sm (cm/s)	$13.7 \pm 3.1$	$13.8 \pm 2.4$	$11.8 \pm 2.6$	$14.7 \pm 2.5^{**}$
Early diastolic, Em (cm/s)	$12.8 \pm 3.9$	$15.2 \pm 3.9^*$	$10.6 \pm 2.9$	$14.0 \pm 2.4^{**}$
Late diastolic, Am (cm/s)	$17.2 \pm 4.9$	$15.9 \pm 4.1$	$18.5 \pm 5.5$	$17.5 \pm 5.3$
Tricuspid E/ Em	$4.1 \pm 2.1$	$3.5 \pm 0.8$	$4.8 \pm 1.7$	$3.5 \pm 0.7^*$
RVEDd (mm)	$34 \pm 5$	$32 \pm 5^*$	$34 \pm 5$	$30 \pm 5^*$
RV systolic pressure (mmHg)	$31 \pm 4$	$30 \pm 5$	$57 \pm 12$	$33 \pm 3^{**}$

\*=  $P < 0.05$ , \*\* =  $P < 0.01$

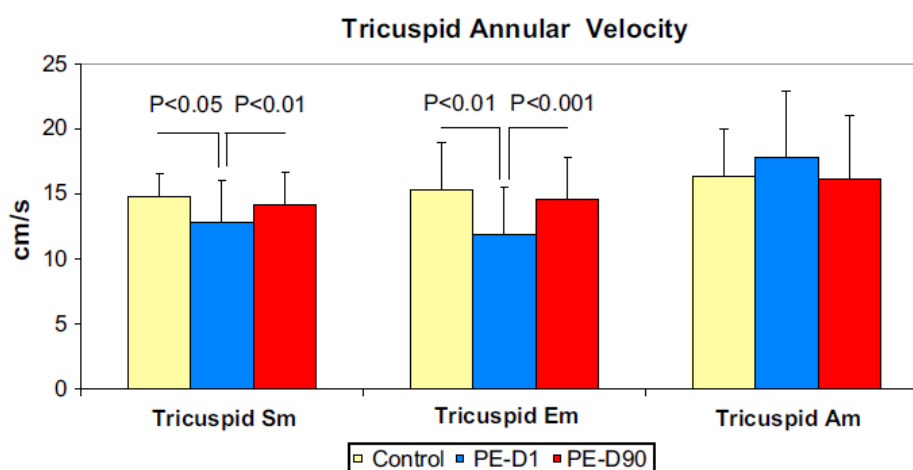
Using a receiver-operating characteristics curve, a tricuspid E/Em cut-off value of  $\geq 4$  provided the best-balanced sensitivity (71%) and specificity (83%) for detecting patients with a right atrial pressure of  $\geq 10$  mmHg (area under the curve = 0.774,  $P = 0.018$ , 95% CI, 59% to 96%). The tricuspid E/Em ratio had a sensitivity of 75% and a specificity of 73% for identifying patients with increased right atrial pressure.

There was a moderate to good correlation between invasive right atrial pressure and right atrial pressure derived from the inferior vena cava ( $r = 0.6$ ,  $P < 0.05$ ). Similar results were also obtained for the correlation between invasive right atrial pressure and the tricuspid E/Em ratio ( $r = 0.6$ ,  $P < 0.05$ ). The calculated PVR for the whole patient group was  $1.8 \pm 0.03$  WU. When separated according to the RV systolic pressure, patients with increased RV pressure had a PVR of  $2.8 \pm 1.1$  WU and patients with normal RV pressure a PVR of  $1.7 \pm 0.3$  WU ( $P < 0.01$ ).

Patients with a positive McConnell's sign showed a decreased tricuspid Sm ( $12.9 \pm 2.9$  vs.  $15.5 \pm 4.0$  cm/s,  $P < 0.05$ ) and tricuspid Em ( $10.9 \pm 2.6$  vs.  $13.5 \pm 5.0$  cm/s,  $P < 0.01$ ) compared to those with a negative McConnell's sign. Also, 78% of patients had increased systolic RV pressure in the presence of a positive McConnell's sign.



**Figure 7.** Tricuspid E/Em ratio as indices of RV diastolic function and filling pressure in healthy subjects and in patients with PE on day 1 and day 90.



**Figure 8.** Comparison of tricuspid Sm, Em, and Am in healthy subjects and in patients with PE on day 1 and day 90.



### 5.3. PAPER III

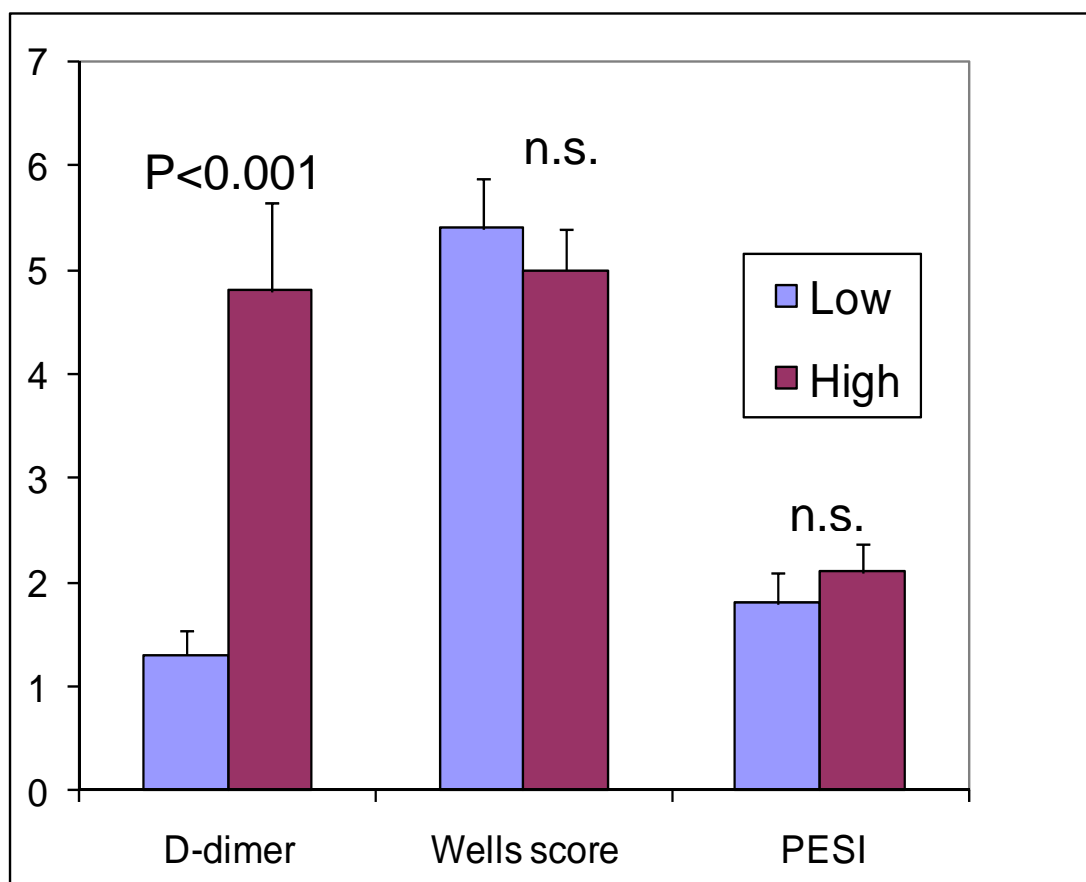
The mean age and the systolic and diastolic blood pressures were as in Paper II. The mean plasma D-dimer concentration was  $3.3 \pm 3.5$  mg/L (range 0.49 - 14.0). Two of the patients had a normal D-dimer. The mean PESI was  $2 \pm 1$ , and the mean Wells score was  $5.3 \pm 1.7$ . Using an ROC analysis, a D-dimer cut-off value of  $\geq 3$  mg/L provided the best-balanced sensitivity (80%) and specificity (77%) in detecting patients with a decreased systolic tricuspid annular velocity (area under the curve = 0.803,  $P = 0.032$ , 95% CI 0.64-0.96).

**Table 8.** Comparison of patients with different D-dimer levels and different PESI.

	D-dimer < 3	D-dimer $\geq 3$	PESI 1-2	PESI 3-5
Number of patients	21	13	23	11
Tricuspid annular velocity (cm/s)				
Systolic, Sm	$13.5 \pm 2.7$	$11.3 \pm 2.7^*$	$15.4 \pm 3.7$	$12.2 \pm 4.0^*$
Early diastolic, Em	$12.8 \pm 3.3$	$10.2 \pm 3.6$	$14.9 \pm 4.1$	$11.5 \pm 4.5$
Late diastolic, Am	$17.2 \pm 3.6$	$18.9 \pm 7.2$	$21.1 \pm 5.9$	$20.1 \pm 7.1$
Tricuspid E/Em	$4.3 \pm 1.8$	$4.9 \pm 2.4$	$3.9 \pm 1.1$	$6.1 \pm 2.9^*$
TAPSE (mm)	$19.9 \pm 4.7$	$16.8 \pm 5.3$	$19.8 \pm 5.4$	$17.2 \pm 5.2$
MPI	$0.5 \pm 0.2$	$0.8 \pm 0.3^{**}$	$0.5 \pm 0.3$	$0.7 \pm 0.4$
RVEDd (mm)	$36 \pm 5.0$	$38 \pm 4.0$	$35 \pm 4.0$	$40 \pm 3.0^{***}$
RV systolic pressure (mmHg)	$37 \pm 12.0$	$58 \pm 13.0^{***}$	$42 \pm 14.0$	$50 \pm 19.0$
PVR (WU)	$1.8 \pm 0.4$	$3.3 \pm 1.1^{***}$	$2.0 \pm 0.6$	$3.5 \pm 1.3^{**}$

\* =  $P < 0.05$ , \*\* =  $P < 0.01$ , \*\*\* =  $P < 0.001$

There was a moderate-to-good correlation between D-dimer and RV pressure ( $r = 0.6$ ,  $P = 0.001$ ) and pulmonary vascular resistance ( $r = 0.68$ ,  $P < 0.001$ ). D-dimer had a fair degree of correlation with MPI ( $r = 0.31$ ,  $P = 0.07$ ) and TAPSE ( $r = -0.31$ ,  $P = 0.07$ ), with borderline significance for both. No significant correlation was found with tricuspid Sm, tricuspid Em or the E/Em ratio. PESI had a fairly good correlation with E/Em ( $r = 0.43$ ,  $P < 0.05$ ) and RV end diastolic diameter ( $r = 0.42$ ,  $P < 0.01$ ), and with borderline significance regarding tricuspid Sm ( $r = -0.30$ ,  $P = 0.07$ ). The Wells score did not correlate significantly with any of the echocardiographic variables.



**Figure 9.** Clinical scoring and D-dimer according to RV pressure are shown in Figure 1. The D-dimer level was higher in patients with RV pressure  $\geq 40$  mmHg compared to patients with RV pressure  $< 40$  mmHg ( $4.8 \pm 3.3$  mg/L vs.  $1.3 \pm 0.9$  mg/L,  $P < 0.001$ ). Both the Wells score and PESI were similar with respect to the RV pressure level.

**Table 9.** Distribution of patients according to D-dimer levels and PESI class. Fisher's exact test  $P = 0.06$ .

	PESI 1-2	PESI 3-5	Total
D-dimer $< 3$	17	4	21
D-dimer $\geq 3$	6	7	13
Totals	23	11	34

D-dimer expressed in mg/L.

Four of the patients with D-dimer < 3 mg/L had a high PESI class. All four of these patients were males and three of them had cancer, adding 10 points and 30 points, respectively, to their PESI scores. Only one additional patient in the whole patient cohort had cancer. The age of the four patients did not differ from that of the whole cohort of patients, or from the patients with a high PESI score and high D-dimer.

## 5.4. PAPER IV

The mean age of the patients was  $63 \pm 13$  years, the heart rate  $89 \pm 21$  beats/min, and the systolic and diastolic blood pressures were  $144 \pm 16$  mm Hg and  $86 \pm 13$  mm Hg, respectively. The myocardial performance index for the whole patient group was  $0.6 \pm 0.3$ .

**Table 10.** Comparison of echocardiographic findings between healthy controls and patients on admission.

	Healthy	Patients
Number of patients	23	15
Tricuspid annular velocity (cm/s)		
Systolic, Sm	$14.8 \pm 1.8$	$14.8 \pm 4.7$
Early diastolic, Em	$15.3 \pm 3.6$	$13.1 \pm 5.0$
Late diastolic, Am	$16.4 \pm 3.6$	$21.1 \pm 6.4^{**}$
Tricuspid E/Em	$3.5 \pm 0.7$	$5.8 \pm 2.6^{***}$
TAPSE (mm)	$26.0 \pm 4.0$	$20.0 \pm 5.0^{***}$
TAPDE (mm)	$10.0 \pm 2.0$	$11 \pm 3.9$
RVEDd (mm)	$24.0 \pm 3.0$	$38 \pm 5.9^{***}$
RV/LV ratio	$0.51 \pm 0.08$	$0.86 \pm 0.18^{***}$

\*\* =  $P < 0.01$  and \*\*\* =  $P < 0.001$

Pulmonary vascular resistance and systolic RV pressure in patients were  $2.1 \pm 0.7$  WU and  $40 \pm 13$  mmHg, respectively. The mean perfused area for the whole patient group was  $6769 \pm 982$  pixels (range 4173 - 8104), and the mean maximal count intensity value was  $40 \pm 9$  (range 29-64). The mean values for the reference group were  $7669 \pm 291$  pixels and  $26 \pm 1.8$ , respectively.

There was very good to excellent correlation between perfused area and pulmonary vascular resistance ( $r = -0.86$ ,  $P < 0.05$ ). Also, a moderate-to-good correlation was seen with RV pressure ( $r = -0.68$ ,  $P < 0.05$ ), tricuspid Em ( $r = 0.62$ ,  $P < 0.05$ ), and RV/LV ratio ( $r = -0.55$ ,  $P < 0.05$ ). Perfused area correlated inversely with RV pressure, pulmonary vascular resistance, and the RV/LV-ratio. The maximal count intensity correlated inversely and significantly with Tricuspid Em ( $r = -0.57$ ,  $P < 0.05$ ), and significantly with the RV/LV-ratio ( $r = 0.76$ ,  $P < 0.01$ ), but not significantly to pulmonary vascular resistance ( $r=0.71$ ,  $P=0.11$ ) or RV pressure ( $r=0.50$ ,  $P=0.14$ ) although both of the latter parameters showed moderate correlation with the maximal intensity.

**Table 11.** Patients with different levels of perfusion, and healthy subjects.

	Perfusion < 10%	Perfusion $\geq$ 10%	P value
Number of patients	8	7	
Tricuspid annular velocity (cm/s)			
Systolic, Sm	17.0 $\pm$ 4.4	12.2 $\pm$ 3.7*	0.01
Early diastolic, Em	16.0 $\pm$ 4.3	10.1 $\pm$ 3.7**	0.02
Late diastolic, Am	23.3 $\pm$ 5.8*	18.5 $\pm$ 6.1	0.09
Tricuspid E/Em	4.9 $\pm$ 1.5**	6.7 $\pm$ 3.1***	0.34
TAPSE (mm)	22.7 $\pm$ 4.8	17.3 $\pm$ 4.0***	0.04
TAPDE (mm)	10.3 $\pm$ 3.6	11.0 $\pm$ 4.1	0.80
RV/LV ratio	0.78 $\pm$ 0.14**	0.94 $\pm$ 0.18***	0.22
MPI	0.5 $\pm$ 0.3	0.6 $\pm$ 0.3	0.92
RV end-diastolic dimension (mm)	37 $\pm$ 6.0***	38 $\pm$ 5.0***	0.70
RV systolic pressure (mmHg)	36 $\pm$ 12.0	43 $\pm$ 13.0	0.17
PVR (WU)	1.8 $\pm$ 0.2	2.7 $\pm$ 0.3	0.17
Maximal count intensity	34.5 $\pm$ 3.5	47.2 $\pm$ 7.7	0.002

\*= $P < 0.05$ , \*\* =  $P < 0.01$  and \*\*\* =  $P < 0.001$  compared to healthy subjects regarding echocardiographic variables.

## 6. STATISTICS

Data are presented as the mean and SD. All P values presented are two-tailed and values  $< 0.05$  were regarded as statistically significant in all studies.

Differences between groups were tested using Student's unpaired and paired t-test in **Paper I** and Mann-Whitney's non-parametric test for unpaired comparisons and Wilcoxon's test for paired comparisons in **Papers II** and **III**. In **Paper IV**, the Kruskal-Wallis non-parametric test was used for comparisons between patients with a loss in the perfusion area of  $\geq 10\%$  or  $< 10\%$  of reference and with healthy subjects. Due to a relatively small patient cohort, non-parametric tests were used in **Papers II, III** and **IV** in order to avoid overestimation of the study results.

Fisher's exact test was applied in **Paper III** to analyse proportions of patients at different D-dimer levels and PESI classes.

Pearson's correlation coefficient ( $r$ ) and Spearman's  $s$  rank correlation coefficient ( $r_s$ ) were used for computation of correlations. Spearman's rank correlation coefficient was used to study relations between continuous and categorical variables in **Paper III** and Pearson's correlation coefficient was used for relations between continuous variables.

The area under the curve (AUC) was calculated using receiver-operating characteristic (ROC) curves to assess the best diagnostic cut-off values of tricuspid E/Em in **Paper II** and of D-dimer in **Paper III**.

Reproducibility was assessed in 20 randomly selected patients in **Papers I** and **II**. In **Paper I** the recorded tricuspid annular excursion parameters were analysed by an investigator on two different occasions without knowing the result from the previous analysis and, in **Paper II**, the recorded DTI parameters were analysed by one investigator on two different occasions and by another investigator on one occasion without prior knowledge of the clinical data or the result from the previous analysis. Variability was expressed as the mean percent error, derived as the absolute difference between the two sets of observations, divided by the mean of the two sets of observations.

All statistical analyses were performed using of the SPSS software package version 15 or higher (SPSS, Chigaco, IL, USA) and were carried out by the study investigators.

## 7. DISCUSSION

### Clinical considerations

Most clinicians are familiar with the problems of diagnosing PE. There are no PE-specific symptoms or signs exclusively pointing to the right direction. Indeed, the most usual clinical symptoms associated with PE could easily be a sign of another disease entirely. Also, the prognosis for untreated PE patients is poor (81-82). These factors have led to the creation of different clinical pre-test probability scores (85-86, 108) to help to identify patients with PE and to predict their outcome. In **paper III**, the Wells pre-test probability score and the PE severity index (PESI) were used to classify patients. The Wells probability score for PE was first published in the late 1990s, and at the beginning of the millennium 2000 an algorithm including D-dimer was presented (86). The problem with this approach is that both the Wells score and D-dimer can be elevated due to other diseases as well and are therefore considered to be non-diagnostic. In today's clinical practice a combination of a low Wells score and a negative D-dimer has been used successfully to exclude patients with clinically significant PE. The clinical probability also facilitates the interpretation of diagnostic tests. The PESI was introduced in 2005 by Aujesky et al. in an attempt to develop a prognostic model for PE. The Model included 11 routinely available clinical parameters at the time of presentation. Since then the PESI has also been validated by others (100). Some studies have shown an association between the PESI and mortality (100, 109). The PESI classification is used to identify low-risk patients who could be managed in an outpatient setting. Another diagnostic parameter discussed in **paper III** is D-dimer. D-dimer is a fibrin degradation product with a specific diagnostic time-frame (110). For purposes of diagnosing PE, the D-dimer is usually indicated in patients with low or moderate pre-test PE probability, whereas in patients with high probability, D-dimer is considered to be of limited value (111). Low or negative results on a high-sensitivity D-dimer alone has been used to reliably rule out PE (112), whereas substantially elevated D-dimer levels have shown an association with a higher clot burden, adverse outcome, and more proximal thrombus location in PE patients (113-114). RIETE investigators studied the association between D-dimer levels and patient outcome and demonstrated increased all-cause mortality as the D-dimer level increased from 2.7% in the first quartile to 7.0% in the fourth quartile (115). The specificity of an increased D-dimer level is known to be reduced in hospitalized patients (116) in whom D-dimer is not recommended as a PE diagnostic tool. In **paper III**, all patients were enrolled at the emergency department and were carefully screened for concomitant diseases. The concept of

using elevated D-dimer levels to predict cardiac dysfunction is relatively new. Some previous studies explored cardiac biomarkers in relation to RV function (97, 117). To our knowledge, there were no published papers investigating the association between D-dimer, clinical pre-test probability scores and RV dysfunction using quantitative echocardiographic techniques at the time when **paper III** was written. We discovered that an elevated D-dimer value  $\geq 3$  mg/L was associated with lower tricuspid Sm and higher MPI indicating RV dysfunction. Patients with higher D-dimer levels also showed increased RV pressure and pulmonary vascular resistance, indicating a greater afterload imposed on the right ventricle in these patients, thus offering an explanation for the impaired RV function. There was also a relatively good correlation between D-dimer and RV pressure and between D-dimer and pulmonary vascular resistance. D-dimer could not distinguish patients with D-dimer levels  $\geq 3$  mg/L from those with D-dimer levels  $< 3$  mg/L regarding purely diastolic parameters such as tricuspid Em and Am or parameters associated with filling pressure such as tricuspid E/Em. In addition, the right ventricle was equally dilated regardless of D-dimer levels. The PESI, when combined with D-dimer, did not contribute any additive value to the evaluation of haemodynamics in acute PE, but did demonstrate an association between higher PESI classes and disturbed RV function indicated by lower tricuspid Sm, higher tricuspid E/Em and a larger RV end-diastolic dimension in patients in higher PESI classes. Pulmonary vascular resistance was significantly higher in PESI classes 3-5, compared with PESI classes 1-2, in agreement with the higher burden on the right ventricle.

## **Echocardiography**

The haemodynamic status at the time of presentation of acute PE is the strongest prognostic predictor of short term mortality (82). In most clinical algorithms, patients suspected to have non-high-risk PE are further investigated with a confirmatory imaging study, most frequently computed tomography of the pulmonary arteries (CTPA), a perfusion/ventilation lung scan, or a pulmonary angiogram. The newest guidelines downgrade the pulmonary angiogram and give priority to CTPA as the preferred diagnostic technique for PE (74). Echocardiography is not included in the diagnostic strategy for non-high-risk PE patients in the guidelines (74) due to its limited reported sensitivity of 60-70%, but there are some recent papers that question this approach (118). Contrariwise, in the suspected high-risk PE patients with hypotension or shock, echocardiography plays a major role in the guidelines. Detection of RV dysfunction or overload, or cardiac thrombi, will be decisive in the choice of treatment and carries a poor

prognosis. In the absence of signs of the RV dysfunction, echocardiography may be useful for the differential diagnosis.

The importance of the RV function in the prognosis of PE has recently been recognised even in haemodynamically stable patients in whom RV dysfunction has been shown to be an independent predictor of short-term and long-term mortality (119-120). Most PE patients with adverse outcomes maintain a normal systolic blood pressure shortly before cardiovascular collapse. Approximately 27% to 55% of PE patients with preserved systemic arterial pressure have been shown to have echocardiographic signs of RV dysfunction (98-99, 121). A recent study showed a short-term mortality in PE patients with and without RV dysfunction of 10% and 3%, respectively, and with a negative predictive value for all-cause death of 97% in association with RV dysfunction (94). Patients with RV dysfunction in combination with elevated cardiac biomarkers as a sign of injury appear to have a particularly high risk of short-term mortality (122). Thus, risk stratification, based on clinical features and markers of RV dysfunction or injury should be used to differentiate between patients with preserved arterial systemic pressure and a low risk of early complication and those in risk of adverse clinical effects. Also, the risk stratification in non-high-risk PE patients should be done within 24-48 hours after admission as recurrent PE or PE-associated complications generally occur early on (123). In our prospective studies, all patients were investigated by echocardiography within 24 hours after arrival at hospital, and in **papers I** and **II** also after 3 months.

One problem with echocardiography when investigating its value in the diagnosis and prognosis in PE is the lack of standardization of echocardiographic criteria for RV dysfunction. A variety of different echocardiographic parameters have been proposed for detecting RV dysfunction and have lead to difficulties in choosing the correct parameter or parameters for a specific diagnosis and in specific situations. Also, there is a growing demand for a simple, user-friendly approach to detect the RV dysfunction in order to allow a non-expert reader to accurately interpret the echocardiographic findings.

### **Right ventricular dimension**

Some investigators suggest that RV-to-LV end-diastolic diameter ratio may be a suitable parameter for diagnosing RV dysfunction in PE patients (122, 124). As shown in **papers I, II** and **IV**, the RV end-diastolic diameter was larger in patients than in healthy subjects, but it could not distinguish patients when classified according to RV pressure (**papers I-II**), D-dimer levels (**paper III**) or levels of pulmonary perfusion loss due to PE (**paper IV**). Only PESI, in



**paper III**, could detect a difference between higher and lower PESI classes in regard to RV end-diastolic diameter. In accordance with Frank-Starling's law, when opposed to an increased workload, the right ventricle attempts to improve its performance by dilating at the early stages. We studied the parameter RV/LV end-diastolic diameter ratio in **paper IV** and found it to be higher in patients than in healthy subjects, and also to be higher in patients with greater pulmonary perfusion losses. The RV/LV ratio showed a moderate and inverse correlation with the perfused lung area in that study. An RV/LV ratio of  $> 0.9$  has been shown to have prognostic value in predicting in-hospital and 30-day mortality (122). In the task force criteria from 2008, the RV/LV ratio is discussed as one of the echocardiographic parameters indicative of RV dysfunction, but it is not considered to take priority over other parameters.

### **Systolic RV function by M-mode echocardiography**

In **studies I** and **II** two echocardiographic techniques were used to assess RV function in acute PE patients, the M-mode derived tricuspid annular plane excursion and the tricuspid annular myocardial velocity by pulsed-wave Doppler tissue imaging (DTI). Studies during the 1990s and earlier used mostly qualitative echocardiographic assessments of RV wall motion, which was judged to be normal or mildly, or moderately, or severely hypokinetic, to determine RV function. The quantitative echocardiographic parameters included the 2D-measured RV/LV end-diastolic ratio, the RV end-diastolic diameter, and Doppler-measured signs of pulmonary hypertension such as increased pulmonary artery systolic pressure and a high tricuspid regurgitant velocity. Also, TAPSE, the tricuspid annular plane systolic excursion was introduced in some earlier PE studies as a RV function parameter, and it has been used ever since to a variable degree in scientific papers to detect RV dysfunction. TAPSE measures the longitudinal motion of the tricuspid annulus towards the apex during systole and represents global systolic RV function. TAPSE is a quick, repeatable measuring method that does not require post-processing or expertise. A good correlation between TAPSE and the RV ejection fraction derived from radionuclide ventriculography, as well as between TAPSE and RVFAC, has been demonstrated (125-126). A recent study acknowledged that TAPSE was not only dependent on RV function but also on that of the left ventricle, thus illustrating ventricular interdependence (47). It has also been shown that TAPSE is prognostically important in PE and in pulmonary hypertension (125, 46). **Study I** explored the tricuspid annular plane excursion both in systole and in diastole in PE patients, and also its relationship with RV systolic pressure. Interestingly, not only patients with high RV systolic pressures, but also those with normal RV systolic pressures, had decreased TAPSE, indicating RV dysfunction even in patients with a

normal RV pressure. TAPSE was further decreased with more markedly increased RV systolic pressure. Thus, the right ventricle was more disturbed in patients with higher RV afterloads. There was, however, only a weak correlation between TAPSE and RV systolic pressure, indicating that the systolic pressure may decline when the right ventricle fails. Also, there was a considerable overlap between PE patients and healthy subjects regarding TAPSE, but none of the healthy patients had decreased TAPSE. Thus, decreased TAPSE is a sign of RV dysfunction but cannot exclude PE. TAPSE improved significantly during follow-up, but it was still not totally normalized after 3 months.

### **Diastolic RV function by M-mode echocardiography**

In accord with **paper I**, a previous study showed that the contribution of the right atrial contraction to total TAPDE is useful in determining RV diastolic function (127). The right atrial contraction to total TAPDE showed a similar trend to that of TAPSE, being more disturbed in patients than in age-matched healthy subjects. Indeed, when comparisons are made, it is mandatory that the age of the patients is in conformity with that of the healthy subjects as the percentage of tricuspid relaxation due to atrial contraction to total TAPDE increases with increasing age (128). The atrial contraction to total TAPDE normalized after 3 months, also suggesting an impairment of RV diastolic function in the acute stage. At the time when the paper I was written, no previous studies had discussed TAPDE as means of assessing the RV diastolic function in PE patients.

### **Right ventricular velocities by DTI**

In **paper II**, pulsed-wave DTI was applied to establish whether further information could be extracted from myocardial velocity data as compared with annular movement in regard to RV dysfunction. Also, an attempt was made to use the ratio of E/Em ratio as a non-invasive parameter for RV filling pressure, as suggested in earlier studies (58, 60), and to compare it with other non-invasive and directly invasive measurements of right atrial pressure. Pulsed-wave DTI is independent of the RV geometry, does not require the visibility of the whole RV free wall, and is not handicapped by the need for correct endocardial border detection. It is also feasible in nearly all patients, which is illustrated by the results in **papers II, III** and **IV**, where all DTI data from patients acquired from the lateral tricuspid annulus region could be analysed, and the data obtained from the mid-portion of the RV free wall in **paper II** was of acceptable quality in 32 out of 34 patients. Due to the attainment of similar velocities at the annular or mid-site of the right ventricle, only annular velocities were used in **papers II, III** and **IV**. Pulsed-

wave DTI is also a reasonably quick and simple method, highly reproducible, and provides excellent temporal resolution and a good signal-to-noise ratio, and there is no need for post-processing, therefore making it quite suitable for PE patients. The intraobserver and interobserver variability of tricuspid Sm, Em and Am were assessed in **paper II** and were found to be low. Moreover, pulsed-wave DTI has been validated by several non-invasive methods (54, 56, 126) and has been used in different patient groups to assess RV systolic and diastolic function (54, 129). A recent study compared different echocardiographic parameters with the MRI-derived global RV ejection fraction and showed the strongest correlation with tricuspid Sm (56). RV function has a complex contraction pattern and is affected by the LV performance through the mechanisms of ventricular interdependence. The contribution of the interventricular septum to the RV function is considerable (130). In recent study using a multisegmental approach, both the lateral and the septal annular tricuspid Sm were measured and compared with the MRI-derived RV and LV ejection fractions. As expected, the lateral annular site was less affected by LV performance than that of the septal site, which was almost equally influenced by the RV and LV ejection fractions. Also, the study concluded that only tricuspid lateral Sm predicted the RV ejection fraction when RV function was disturbed and LV function was preserved, or vice versa (131). In **paper II** the left ventricle was included in the analysis showing septal and lateral mitral annular velocities in parity with values in healthy controls and reflecting normal LV systolic function, supported by normal LV ejection fractions in patients.

In **paper II** tricuspid Sm was decreased in comparison with healthy subjects, thus reflecting RV dysfunction in the acute stage. When divided into groups according to RV systolic pressure, patients with an increased RV pressure showed further a decrease in tricuspid Sm, thus reflecting the even more disturbed RV functions in this subgroup.

### **Pulmonary vascular resistance and perfusion defects**

The extent of the pulmonary vascular obstruction is crucial for the increase in pulmonary vascular resistance and, thereby, for the prognosis in PE patients. Patients in **paper II** with high RV pressures were also shown to have augmented pulmonary arterial resistance ( $> 2.0$  WU), determined non-invasively using the formula introduced by Abbas et al. (132), being indicative of the higher degree of afterload on the right ventricle and suggesting that the impaired RV function was caused by pulmonary vascular obstruction. Significantly greater perfusion defects have been demonstrated in acute PE patients with RV dysfunction compared with those with normal RV wall motion (121). Previous studies have, however, shown evidence of RV dysfunction only with substantial perfusion losses, and other ones have failed to demonstrate

any significant correlation at all (121, 99, 133). **Paper IV** found a lower tricuspid Sm already in patients with a reduction in perfused area of  $\geq 10\%$ . Thus, even patients with a relatively small perfusion loss were associated with RV dysfunction. In **paper IV**, pulmonary arterial resistance also tended to be higher in patients with a perfused area reduction of  $\geq 10\%$ , with a mean value of  $> 2$  WU, compared to those with a perfused area reduction of  $< 10\%$ , thus indicating a significant difference in afterload between the two groups. There was also a good inverse correlation between pulmonary arterial resistance and the relative loss of perfusion area. A good correlation was also seen between the simple, maximum count intensity method which reflects perfusion inhomogeneity and the scintigraphic perfused area. Some earlier studies have suggested a cut-off value of perfusion defects of  $\geq 30\%$  as an indication to perform echocardiography for identification of RV dysfunction in haemodynamically stable patients (121). With such an approach, however, some patients with RV dysfunction would be missed and be at risk of a worse outcome due to misclassification. Results from **paper IV** seem to suggest that echocardiography should be extended to a larger number of non-high-risk PE patients.

### **Myocardial performance index**

In **paper II** the whole patient cohort had a lower tricuspid Sm than healthy subjects but when divided according to RV systolic pressure, patients with normal RV pressures did not differ from healthy subjects. The same was true for the MPI, another echocardiographic parameter shown to be an independent predictor of RV function (62). The MPI was shown to be higher in the whole patient group compared to normal values reported by others (57), and was even further increased in patients with elevated RV systolic pressures, indicating RV dysfunction due to a larger RV burden in these patients, whereas patients with normal RV pressures showed similar values to those reported in healthy subjects. The MPI also showed a fairly good correlation with D-dimer and was shown to be significantly increased in patients with higher D-dimer levels in **paper III**, providing further evidence of a high burden on the right ventricle in patients with an elevated MPI. The MPI includes both systolic and diastolic cardiac time intervals. As myocardial function deteriorates, ejection time is shortened and the pre-ejection and isovolumic relaxation periods are lengthened. A previous study found MPIs  $> 0.40$  to have high sensitivity and a negative predictive value for detecting abnormal RV function (134). In **papers II, III and IV**, MPI had a value of  $\geq 0.6$  for the whole cohort of PE patients, with even higher values in patients with increased RV systolic pressures, which are well over

the suggested MPI level. According to these findings, by using an MPI cut-off value of  $> 0.40$  RV dysfunction should not be missed.

### **Diastolic right ventricular function**

Although there are growing numbers of papers discussing RV diastolic function, its significance in different clinical conditions is not fully understood. There are also discrepancies regarding the parameters used in different papers, and the results obtained therewith (22, 52, 135). The acute increase in afterload in PE patients increases RV wall tension and may lead to diastolic and systolic functional impairment. **Paper II** showed lower tricuspid Em values in all patients including those with normal RV systolic pressures, normal tricuspid Sm and normal RV filling pressures, reflecting disturbed RV diastolic function in all patients compared with healthy subjects. Thus, a normal tricuspid Sm or MPI alone should not be used to exclude disturbed RV function. **Paper IV** demonstrated a moderate association between perfused area and tricuspid Em and significantly decreased Em in patients with a reduction in perfused area of  $\geq 10\%$ . Furthermore, all patients showed a high tricuspid E/Em ratio compared to healthy subjects, with further increases with a greater reduction in perfused area reflecting the higher filling pressures in these patients. The E/Em ratio was further explored in **paper III** and was significantly elevated in patients in PESI classes 3-5, but not in PESI classes 1-2, thus separating the classes regarding filling pressure. The whole patient cohort had an elevated E/Em ratio compared to healthy subjects in **paper II**, with even further increased values in patients with high systolic RV pressures which normalized after 3 months. On the other hand, patients with normal RV pressures did not differ in the tricuspid E/Em ratio between the acute stage and follow-up. The tricuspid E/Em ratio showed a moderate to good correlation with the invasively and non-invasively measured right atrial pressure in **paper II**. A previous study showed a good correlation between invasively measured right atrial pressure and the E/Em ratio irrespective of RV function and both in patients with and without mechanical ventilation (60). Another recent study also concluded that the E/Em ratio was useful for non-invasive estimations of RV filling pressure and for detecting serial changes but used a different cut-off value to determine elevated right atrial pressures and found the E/Em ratio to be weakly correlated with the right atrial pressure in patients with normal RV function or early on after cardiac surgery (131). In an earlier study, an increase in right atrial pressure was indicative of a severe degree of RV outflow impedance and appeared to increase as a direct response to elevated pulmonary arterial pressures (101). In **paper II**, the E/Em ratio had relatively good sensitivity and specificity in identifying patients with increased right atrial pressures.

According to our findings, tricuspid Em is an early marker of disturbed RV function in PE patients and could be used to monitor patients, but its prognostic significance is still unclear and it should be further investigated. No correlation between tricuspid Am, the late diastolic component of tricuspid myocardial velocities, and RV filling pressure was found in **paper II**. Similarly, a previous study could not establish a relationship between tricuspid Am and right atrial pressure, suggesting tricuspid Am to be a function of a complex interaction of RV end-diastolic pressure, RV relaxation, and right atrial systolic function (58). Tricuspid Am was similar in patients irrespective of the RV pressures than in healthy subjects in **paper II**, and could not differentiate between patients with D-dimer levels of  $\geq 3$  mg/L or  $< 3$  mg/L, or patients with a high or low PESI class in **paper III**.

### **Left ventricular function in PE**

**Paper II** also revealed that mitral septal and lateral annular Em was reduced in patients, compared to healthy subjects, as was the transmitral E/A ratio, all reflecting the disturbed LV diastolic function in patients. Impaired LV relaxation may be explained by the displacement of the interventricular septum towards the left ventricle when the right ventricle dilates as a response to a sudden increase in afterload. Also, due to the relatively stiff pericardium, the sum of the two ventricles cannot change in the acute phase.

### **McConnell's sign as an indicator of PE**

McConnell's sign has been suggested in some previous papers and guidelines to be a PE-specific parameter revealing a specific contraction pattern in the RV free wall, including abnormal motion of the mid-free wall with normal wall motion at the apex (37). The normal motion of the apex in PE patients has been questioned recently, some studies suggesting the apical motion to be due to passive movement rather than being a sign of active contraction. Also, subsequent study could not confirm the previous findings by McConnell et al. (38). In **paper II** myocardial velocities of the mid-portion of the RV free wall were similar to those obtained from close to the tricuspid annulus both in systole and in diastole, thus not supporting the notion of a specifically depressed mid-portion in PE patients. Moreover, measurements of apical myocardial velocities were technically poor compared with the other sites and were difficult to interpret. In **papers I and II**, McConnell's sign had a sensitivity of only approximately 25% in detecting patients with PE. Therefore, it should not be used as a single parameter in suspected PE patients. In both papers, patients with a positive McConnell's sign showed a greater influence on echocardiographic parameters. In **paper I** TAPSE was more

decreased in patients with a positive McConnell's sign and they also had higher RV pressures compared with patients with a negative McConnell's sign. The same was true in **paper II** with more deranged tricuspid Sm and Em, reflecting disturbed RV function in systole as in diastole, and above that, borderline significant increase in E/Em indicating higher RV filling pressure in patients with positive McConnell's sign. Thus, positive McConnell's sign may give valuable hemodynamic information in the acute stage.

## 8. CONCLUSIONS

- 1) Tricuspid annular plane excursion measured by M-mode showed an impairment of the RV systolic and diastolic function at the acute stage. Abnormal systolic RV function was seen even in patients with normal RV systolic pressure.
- 2) Pulsed-wave Doppler tissue imaging is feasible in all PE patients and may be used to determine RV function and filling pressure. The tricuspid early diastolic velocity may be used as an early marker of RV dysfunction even in patients with normal systolic RV function, normal RV systolic pressure, and normal RV filling pressures.
- 3) A specific cut-off value of D-dimer and a certain level of pulmonary perfusion loss may identify patients with RV dysfunction, and thereby help to determine their risk profile. Pulmonary embolism severity index showed no additional value to D-dimer. In patients with normal systemic blood pressure signs of RV dysfunction may occur already at a relatively small perfusion loss.
- 4) Haemodynamically stable patients with acute pulmonary embolism may show echocardiographic signs of RV dysfunction. Therefore, echocardiography could add valuable information in a number of non-high-risk PE patients.



## 9. SAMMANFATTNING PÅ SVENSKA

Venös tromboembolism (VTE) manifesteras ofta som djup ventrombos eller lungemboli (LE). VTE är ett multifaktoriellt tillstånd med interaktion mellan hereditära och förvärvade risk faktorer. Den kliniska bilden vid LE är ospecifik. LE inträffar då en trombmassa lossnar från bildningsstället i en ven och med cirkulationen förs till lungkretsloppet. Obstruktionen av lungkärlen är både mekanisk beroende av själva trombmassan och vasokonstriktiv, vilket ytterligare ökar flödesmotståndet i lungkretsloppet. En normal höger kammare kan inte utan vidare hantera situationer med akut förhöjda tryck i lilla kretsloppet. Som svar på ett ökat tryckarbete ökar väggtemperaturen i höger kammare åtföljt av dilatation, nedsatt myokardperfusion, hypokinesi och sekundärt läckage i tricuspidalisklaffen. Massiv lungembolisering hos en hjärt-lung frisk individ omfattande cirka halva lungkärlsbädden kan leda till högerkammersvikt. Är lungcirkulationen redan påverkad kan även mindre embolier ge högerkammardysfunktion. Högerkammardysfunktion ses även hos patienter med bibehållet systemiskt blodtryck och har prognostisk betydelse. Ekokardiografi är en ofta använd metod för bedömning av högerkammarfunktionen och är därigenom till hjälp vid riskstratifiering av patienterna.

### ARBETE I

I studie I undersöktes 40 patienter med avancerad ekokardiografi inom 24h från ankomst till sjukhus. Högerkammardimension och systolisk respektive diastolisk funktion bedömdes med hjälp av AV-plansmetoden och jämfördes med kammarfunktionen hos friska ålderskontroller. Både systoliska och diastoliska högerkammarfunktionen var sänkt hos patienterna jämfört med kontrollerna. Patienterna med högre tryck i lungkretsloppet hade sämst kammarfunktion. Den diastoliska funktionen återhämtade sig snabbare än den systoliska som fortfarande var något nedsatt jämfört med kontrollerna efter tre månader.

### ARBETE II

I studie II bedömdes högerkammarfunktionen med hjälp av vävnadsdoppler (DTI) under systole och diastole. Den tidig-diastoliska vävnadshastigheten visade sig vara lägre hos samtliga patienter jämfört med kontrollerna, även hos patienterna som hade normal systolisk kammarfunktion, normalt maxsystoliskt tryck i lungkretsloppet och normala fyllnadstryck i

höger kammare. Således skulle man kunna använda den tidig-diastoliska vävnadshastigheten som tidig markör för högerkammardysfunktion och för monitorering av patienterna. Den största påverkan av vävnadshastigheterna hade patienterna med högt systoliskt högerkammertryck, vilka även hade de högsta nivåerna av fyllnadstryck.

### **ARBETE III**

Studie III beskriver relationen av D-dimer till vävnadsdoppler i akutskedet. Det fanns en tydlig försämring i högerkammerfunktionen med högre koncentrationer av D-dimer i blodet och ett gränsvärde av D-dimer för identifiering av patienter med högerkammarpåverkan konstaterades. Patienter med högre D-dimer nivåer hade också betydligt högre högerkammertryck och lungkärlesresistans. Gängse kliniska scoringsystem visade sig inte bidra ytterligare till identifiering av kammarpåverkan hos LE patienterna.

### **ARBETE IV**

I studie IV undersöktes graden av perfusionsnedsättning i lungorna, bestämd med isoptopteknik vid akut lungemboli och dess inverkan på ekokardiografiska variabler för högerkammerfunktion. Patienterna med större perfusionsbortfall hade nedsatt högerkammerfunktion och visade tendens till högre högerkammertryck och lungkärlesresistans vid jämförelse med patienter med mindre perfusionsbortfall. Lungperfusionen hade en tydlig relation med lungkärlesresistans, högerkammertryck och kvoten mellan höger- och vänsterkammarediametrar. Påverkad högerkammerfunktion sågs redan hos patienter med små perfusionsdefekter.

Sammanfattningsvis visar avhandlingen att även patienter med akut lungemboli som inte är hemodynamiskt påverkade vid ankomsten till sjukhuset, kan ha ekokardiografiska tecken till högerkammardysfunktion. Den diastoliska kammarfunktionen tycks påverkas tidigare än det systoliska, även hos patienter med till synes normalt systolisk högerkammertryck, och skulle således kunna användas för monitorering av patienterna. En viss nivå av D-dimer i blodet och en viss grad av perfusionsbortfall vid lungscintigrafi skulle kunna visa sig värdefulla för identifiering av patienter som behöver mer noggrann utredning och uppföljning.

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