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Point-of-Care Echocardiography and Electrocardiography in Assessing Suspected
Pulmonary Embolism

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of
the Requirement for the Degree of Doctor of Medicine

By

John Grotberg, MS

2018

POINT-OF-CARE ECHOCARDIOGRAPHY AND ELECTROCARDIOGRAPHY IN ASSESSING SUSPECTED PULMONARY EMBOLISM.

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Daniels and TwiST electrocardiogram (ECG) scores have been proposed to detect right heart strain (RHS). Tricuspid Annular Plane Systolic Excursion (TAPSE) is a reliable indicator of RHS in patients with acute pulmonary embolism (PE). I aimed to investigate the relationship between these ECG scores, TAPSE, and the level of care required for patients with acute PE. This was a prospective observational study of 110 patients undergoing CTA for suspected PE. ECGs were obtained and patients underwent bedside echocardiography. Low TAPSE was defined as ≤ 17 mm. Mean Daniels and TwiST scores were compared to mean TAPSE, and all were used to evaluate the risk of requiring "PE elevated care" (PEEC), defined as care more aggressive than simple heparination. Mean Daniels and TwiST scores were significantly different between low and high TAPSE groups ($p < 0.0001$), and high Daniels and TwiST scores correlated to low TAPSE ($p < 0.0001$, $p = 0.0002$). PE positive (PE+) patients had lower mean TAPSE than PE negative (PE-) patients ($p = 0.0003$). PE+ patients had a higher mean Daniels score and mean TwiST score than PE- patients ($p = 0.0024$, $p = 0.0033$). Patients requiring PEEC had lower mean TAPSE ($p = 0.047$) and higher mean TwiST ($p = 0.020$) values. TAPSE ≤ 17 mm and TwiST ≥ 5 had increased risks of 6.9 ($p = 0.045$) and 4.4 ($p = 0.025$) respectively for requiring PEEC. Both the Daniels and TwiST ECG scores correlated with TAPSE. All three were predictive of PE on CTA, while TAPSE and TwiST were predictive of requiring PEEC, suggesting their prognostic value in PE care.

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Table of Contents

1. Introduction.....	6
1.1 Deep Vein Thrombosis and Pulmonary Embolism.....	6
1.1.1 Background.....	6
1.1.2 Pathophysiology.....	7
1.1.3 Diagnostic Evaluation.....	8
1.2 Management of Acute Pulmonary Embolism.....	10
1.2.1 Prevention.....	10
1.2.2 Anticoagulation v. Thrombolysis.....	10
1.2.3 Invasive Therapies for Acute Pulmonary Embolism.....	13
1.2.4 Inhaled Nitric Oxide	13
1.3 Tricuspid Annular Plane Systolic Excursion (TAPSE)	14
1.3.1 Assessment of Right Ventricular Systolic Function	14
1.3.2 Prognostic Value of RV Dysfunction in Pulmonary Embolism	17
1.3.3 Inter-Observer Reliability of TAPSE	20
1.4 Electrocardiography in Acute Pulmonary Embolism	21
1.4.1 Diagnostic and Prognostic Indication: The Daniel Score	21
1.4.2 Correlating Echocardiography and Electrocardiography: TwiST	23
2. Statement of Purpose.....	25
3. Methods	26
3.1 Design	26
3.2 Eligibility Criteria	26

3.3 Echocardiography	27
3.4 Electrocardiography	27
3.5 Prognostic Evaluation: PE Elevated Care (PEEC)	28
3.6 Statistical Analysis	28
3.6.1 Diagnosis of PE	28
3.6.2 Comparison of TAPSE and ECG	29
3.6.3 TAPSE, ECG and PEEC	29
3.6.4 The Role of Research Study Members.....	29
4. Results	30
4.1 Enrollment Demographics and Hospital Course	30
4.2 Diagnosis of PE	30
4.3 Comparison of ECG Scoring and TAPSE Measurements	32
4.4 PEEC v. Non-PEEC	34
5. Discussion	34
6. References	40
7. Figures	46
8. Tables	47

1. Introduction

1.1 Deep Venous Thrombosis and Pulmonary Embolism

1.1.1 Background

Venous thromboembolism (VTE), encompassing both deep venous thrombosis (DVT) and pulmonary embolism (PE), is one of the three leading cardiovascular causes of death, with the other two leading causes being myocardial infarction (MI) and stroke. It is estimated that between 100,000 and 300,000 VTE-related deaths occur annually in the United States. Approximately 75% of symptomatic VTE events are community-acquired, while the remaining 25% are hospital acquired, making the recognition and treatment of VTE essential in both emergency medicine and critical care settings (1). In 1999, the International Cooperative Pulmonary Embolism Registry (ICOPER) examined 2454 consecutive eligible patients with acute PE from 52 hospitals in 7 countries, analyzing all-cause mortalities within 3 months of diagnosis. The overall crude 3-month mortality rate was 17.4%, of which 45.1% were ascribed to PE. In addition, significant prognostic factors included age over 70 years old, cancer, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), systolic arterial hypotension, tachypnea, and right ventricular (RV) hypokinesis on echocardiography (2). Due to the variety of ways patients can present with acute PE, and its often, deadly prognosis, it is often referred to as a great masquerader. It is for this reason that so much research has focused on understanding the pathophysiology, attaining better diagnostic inclusion and exclusion criteria, and determining prognostic factors for risk stratification and

therapy. The bedrock of research in diagnosing acute pulmonary embolism surrounds methods to increase the sensitivity of diagnostic criteria, while also avoiding unnecessary radiation with CT scans, while also incorporating methods to properly stratify patients who may have increased morbidity and mortality.

1.1.2 Pathophysiology

Acute PE has physiological consequences of interfering with both circulation and gas exchange. Gas exchange is disrupted due to inflammatory mediators, resulting in surfactant dysfunction, atelectasis and intrapulmonary shunting along with increased dead space ventilation and V/Q mismatch (3,4), while circulatory changes occur due to mechanical obstruction from the thrombus (or thrombi), as well as PE-induced vasoconstriction from inflammatory mediators and hypoxia, leading to increased pulmonary arterial pressures and vascular resistance (4). Acute increases in pulmonary vascular resistance cause strain on the right side of the heart secondary to the increased pressure required to maintain right-sided cardiac output. Increased pressures in the RV and right atrium leading to RV dilation and systolic dysfunction of the myocardium. As RV contraction time becomes prolonged, bowing of the interventricular septum can result (5), leading to decreased LV filling and decreased cardiac output and cardiac index (CI). Additionally, development of a right bundle branch block (RBBB) can occur secondary to increased pressure on the subendocardial conduction system as well as decreased right coronary perfusion pressure. This can exacerbate the desynchronization of the ventricles, leading to decreased LV filling and hypotension (6). An increase in demand can also lead to RV ischemia (4). The aforementioned pathophysiology can result in a fatal feedback

loop of increased RV pressure and RV dilation, decreased cardiac output, decreased coronary perfusion pressure and increased RV myocardial ischemia, leading to acute RV failure.

1.1.3 Diagnostic Evaluation

In analyzing the current standards for diagnostic evaluation of patients with suspected PE, it is necessary to begin with the history and physical exam. Even before any serologic testing or imaging, patients can be risk stratified for acute PE with PE Rule-Out Criteria (PERC). In particular, PERC coupled with physician gestalt for PE has shown to be a highly sensitive test. The components of the PERC criteria involve the following eight questions (7):

1. Is the patient older than 49 years of age?
2. Is the pulse rate above 99 beats per minute?
3. Is the pulse oximetry reading > 95% while the patient breathes room air?
4. Is there a present history of hemoptysis?
5. Is the patient taking exogenous estrogen?
6. Does the patient have a prior diagnosis of venous thromboembolism (VTE)?
7. Has the patient had recent surgery or trauma (Requiring endotracheal intubation or hospitalization in the previous 4 weeks)?
8. Does the patient have unilateral leg swelling?

In 2008, a large study incorporating more than 8,000 patients across 13 emergency departments evaluated PERC. Among low gestalt suspicion and PERC (-) (answering no to the 8 PERC questions), 15 patients were VTE (+) and one patient died, yielding a false negative rate of 1%. As a diagnostic test, low suspicion and PERC (-) had a sensitivity of 97.4% and a specificity of 21.9% (8), allowing exclusion of PE without D-dimer testing that could lead to unnecessary imaging. Avoiding unnecessary imaging and radiation is an endeavor that has been investigated, and is one that point of care ultrasound can also play a role in risk stratification. In 2012,

the National Quality Forum (NQF) endorsed a performance measure to increase imaging efficiency for evaluation of PE in the ED. The primary outcome was the proportion of imaging that was potentially avoidable according to the NQF measure, as defined by imaging a patient with low pretest probability for PE who either did not have a D-dimer test ordered, or who had a negative D-dimer test result. It was found that one third of imaging could be categorized as avoidable (9). Apart from PERC, additional criteria may include presence of limb, whole-body, or neurologic immobility. Contrary to belief, travel greater than 8 hours was not shown to significantly increase the risk for VTE (10). It should be noted that other scoring systems exist to aid physicians in gestalt for suspecting PE. Notably, the two most commonly used scoring systems are the Wells PE Criteria, as well as the Geneva Score (1). Both scoring systems aid in risk stratifying patients and guiding the need for further diagnostic work up. They overlap in many respects, including aspects of patient history such as age, history of prior DVT/PE, recent surgery and active malignancy (1).

While the use of ECG and bedside echo will be discussed further as diagnostic and prognostic tools in patients with suspected PE, it is also worth briefly discussing the value of laboratory tests. Many laboratory tests also aid in the diagnostic work up of patients with suspected PE, and include troponin, B-type natriuretic peptide, and D-Dimer (11). However, these tests alone can be elevated in other pathologies, and must therefore be added to the entirety of the clinical context surrounding a patient. For example, Kabrhel et al. found that significant positive predictors of elevated D-Dimer in patients evaluated for PE included female sex, increasing age,

black (vs. white) race, cocaine use, neurologic immobility, prior venous thromboembolism, hemoptysis, hemodialysis, active malignancy, and numerous others. On the other hand, several variables known to be associated with PE were not significantly associated with a positive D-Dimer, such as BMI, exogenous estrogen use, thrombophilia, trauma within 4 weeks, and others (12).

1.2 Management of Acute Pulmonary Embolism

1.2.1 Prevention

Naturally preventing PE is an important endeavor. It is critical in reducing the death rate, morbidity, and financial cost of PE. Mechanical measures and pharmacological measures currently exist to aid in its prevention. Mechanical measures include compression stockings, intermittent pneumatic compression devices and placement of temporary or permanent inferior vena cava (IVC) filters. Pharmacological measures include fractionated heparin, low-molecular-weight heparin, warfarin, and fondaparinux (11).

1.2.2 Anticoagulation vs. Thrombolysis

When discussing management of acute PE, it should be mentioned that 3 subtypes exist that depend on certain clinical and/or diagnostic criteria. Massive PE is defined as PE with sustained hypotension (systolic blood pressure < 90 for more than 15 minutes) not due to another cause other than the PE (1). Submassive PE is defined as PE without hypotension, but with evidence of RV dysfunction or myocardial necrosis. This can be evidenced by RV dilation or dysfunction by echocardiography, CT, elevated troponin, elevated BNP, or ECG changes consistent with right heart strain (1). Low risk PE refers to those PEs that do not produce

hypotension or evidence of right heart strain (1). In low risk and submassive PE, the common treatment is heparin-based anticoagulation by continuous infusion with a target partial thromboplastin time of 60-80 seconds, however it is also becoming common for these patients to be treated with Novel Oral Anticoagulants (NOACs) such as rivaroxaban and apixaban, or bivalirudin for patients with heparin-induced thrombocytopenia (HIT), while patients with massive PE often receive thrombolysis by recombinant tissue plasminogen activator (tPA) as 100 mg continuously infused over a 2 hour period (11). However, controversy remains about how to treat patients with submassive PE who are normotensive. In a double-blinded study conducted in 49 centers in Germany by the Management Strategies and Prognosis of Pulmonary Embolism Trial-3 (MAPPET-3), normotensive patients with acute PE were randomly treated with tPA (after excluding bleeding risk) and heparin or placebo and heparin. The primary endpoint examined included death or clinical deterioration. The incidence of primary endpoint was significantly higher in the placebo and heparin group compared to tPA and heparin and the probability of 30-day event free survival was significantly higher in the tPA and heparin group (13). This data echoed earlier data from Goldhaber et al. (14), and has since been discussed in case reports (15,16), in which patients who received tPA had a more rapid reversal of RV dysfunction, and experienced no recurrence of clinical episodes of PE compared to 5 recurrences and 2 deaths in the heparin-alone group.

The rapid improvement and lower incidence of adverse clinical outcomes of patients who received tPA raises the importance of acquiring new methods of risk stratification for emergency department physicians. Identifying the subset of

patients with submassive PE and prognostic indication for poor clinical outcome may aid in driving therapy with tPA if they are low risk for bleeding. While continued research must be performed in the risk for bleeding of patients with acute PE, a study of 104 patients at Brigham and Women's Hospital with acute PE who received tPA was performed, and major bleeding was found in 19.2% of patients. The principal site of bleeding was unknown (45%), while other sites included GI, retroperitoneal, splenic, and intracranial (5%). It was also determined that independent predictors for major bleeding were administration of catecholamines for systemic arterial hypotension, cancer, diabetes mellitus, and elevated international normalized ratio (INR) prior to fibrinolysis (17). These relatively high rates of spontaneous bleeding may have occurred due to many factors, namely the increased average INR in patients who had high risk bleeding events compared to those who did not (1.4 vs 1.1), as well as the small sample size (only 1 patient had an intracranial hemorrhage, which represented 5% of the patients who had a major bleeding event) (17). More recent literature has evaluated whether the dose of 100 mg tPA as a continuous infusion may be increasing the bleeding risk, and has sought to elucidate whether lower doses of tPA can both improve RV function and mortality while also minimizing the risk of spontaneous hemorrhage in patients with submassive PE. A meta-analysis by Zhang et al. showed that decreased doses of tPA (0.6 mg/kg bolus followed by 50 mg/2h) in patients with acute PE was non-inferior in achieving hemodynamic improvement when compared to standard doses of tPA (100 mg), while also yielding a decreased bleeding risk compared to standard tPA

dosing, as well as showing no increased risk in bleeding when compared to heparin alone (18).

1.2.3 Invasive Therapies for Acute Pulmonary Embolism

It should be noted that for patients with contraindications to thrombolysis, catheter-based or surgical embolectomy can be considered if risk stratification indicates a high probability of poor outcome leading to loss of hemodynamic stability (11). The prognosis for open embolectomy has dramatically improved. During its renaissance, newer surgical techniques led to an 89% survival rate of 29 embolectomies performed at Brigham and Women's Hospital within a 2-year period (11). Other invasive strategies include catheter-mediated thrombus fragmentation, rheolytic thrombectomy, catheter-mediated thromboembolus aspiration, and catheter-directed thrombolysis via infusion catheters such as the Endo Wave System (EKOS) (19). Catheter directed thrombolysis has been shown to improve RV function by reducing pulmonary arterial pressures as well as RV pressures while decreasing the risk of adverse bleeding when compared to systemic thrombolysis (19).

1.2.4 Inhaled Nitric Oxide

As previously mentioned, acute PE increases pulmonary arterial resistance, and can lead to right ventricular failure and circulatory collapse. Inhaled nitric oxide (NO) leads to immediate vasodilation of the pulmonary circulation. Inhaled NO is selective to the pulmonary circulation due to its rapid binding and inactivation by hemoglobin. Thus, systemic circulation does not experience vasodilation (20). Thus far, there have been no randomized controlled trials evaluating the effect of inhaled

NO on patients with massive and submassive PE. However, numerous case studies have shown it holds promise, in particular with patients for which tPA may be contraindicated (20-22). For example, Szold et al. found that in four patients suffering from acute massive PE after having abdominal surgery, inhaled NO (20-25 ppm), led an improvement in pulmonary and systemic blood pressures, heart rate and lung gas exchange within minutes after administration (20).

1.3 Tricuspid Annular Plane Systolic Excursion (TAPSE)

1.3.1 Assessment of Right Ventricular Systolic Function

There are several direct and surrogate measures of right heart strain in acute PE, but the quantitative measurement of tricuspid annular plane systolic excursion (TAPSE) has been found to be reproducible and to provide prognostic value in both PE and other disorders. The determination of TAPSE by bedside echo in the Emergency Department has been less well investigated. Due to the limited access to cardiology consults at some hospitals, or due to the amount of time it may take for a consult, early risk stratification by emergency physicians for patients with acute PE may help guide appropriate therapy and prognosis.

The ability to assess RV systolic function in an Emergency Department setting is critical in aiding in the formulation of a diagnosis for patients with undifferentiated dyspnea or pleuritic chest pain, as well as for directing therapy. As previously mentioned, the presence of RV systolic dysfunction is a major indication for thrombolytic therapy and a prognostic indicator in patients with massive or submassive PE (23). 2D echocardiography provides a unique tool that emergency physicians can use at the bedside to assess RV function and acute right heart strain.

Many 2D echocardiography assessments of RV strain, and more specifically RV strain in acute PE, are qualitative in nature, and include RV size compared to LV size, septal flattening, tricuspid regurgitation with color flow Doppler, paradoxical septal motion, diastolic left ventricular (LV) impairment, direct visualization of PE, right ventricular hypertrophy (RVH), a qualitatively plethoric inferior vena cava (IVC), and McConnell's sign (RV free wall hypokinesis with apical sparing) (23-25). In particular, the apical sparing of McConnell's sign has been explained by mechanical tethering of the RV apex to a hyperdynamic left ventricle (24,25). However, cardiologists have sought more quantitative measurements to estimate RV systolic function, many of which have not permeated emergency medicine research and clinical practice.

One such measurement is that of tricuspid annular plane systolic excursion, or TAPSE. The right side of the heart, unlike the left side, contracts along the longitudinal axis of the heart due to the longitudinal direction of RV muscle fibers. This can be visualized on transthoracic echocardiogram (TTE) as the base of the heart ascends toward the apex in a standard apical 4-chamber window. M-mode is then used along the plane of the tricuspid annulus, creating a waveform as the annulus ascends during systole (23) (Figure 1). The TAPSE measurement provides a quantitative value of the linear displacement of the tricuspid annulus between systole and diastole. In terms of its relation to RV systolic function, Ghio et al. determined that TAPSE can be a physiological index of RV function based on RVEF estimates with thermal dilution and cross-sectional areas methods (27). Kaul et al. as well as Ueti et al., showed that tricuspid annulus excursion correlated well to

right ventricular ejection fraction (RVEF), confirmed by radionuclide angiography (28,29). Additionally, Ueti et al. showed a significant inverse correlation between mean pulmonary arterial pressure (MPAP) and RVEF, D wave integral (DWI), peak velocity of D wave (PVDW) and TAPSE. This was interpreted as the well-known relation between pulmonary artery pressure and RVEF in pulmonary, myocardial and valvular heart disease, and results from the dependence of right ventricular systolic function on afterload (29). Miller et al. also found a correlation between TAPSE and RVEF, and high specificity and negative predictive value for detecting abnormal RV systolic function (30). It has also been demonstrated that TAPSE correlates strongly with RV fractional area change (RVFAC), log B-type natriuretic peptide, and pulmonary vascular resistance (PVR). A TAPSE of 17.5 mm was determined to be the best cutoff for detection of RV systolic dysfunction, defined by RVFAC < 30%, with a sensitivity of 87% and a specificity of 91% (23). Furthermore, its correlation to RVFAC has been proven as a useful measurement for RV systolic function regardless of pulmonary artery pressures (31).

However, it should be noted that this still remains an area of contention in the literature and reproducibility of these correlations, as Anderson et al. showed little correlation between combining TAPSE in M-mode and tissue Doppler of the tricuspid annulus (TAPSE-TDI) with RVEF as measured by radionuclide angiography and gated blood-pool single photon electron computed tomography, while fractional area change of the RV and RV myocardial performance index by pulsed-wave Doppler and tissue Doppler correlated well with RVEF (32).

Moreover, it has been suggested that TAPSE alone is not solely dependent on RV systolic function, but also on LV systolic function due to tethering and translational motion of the heart (23). Lopez-Candales et al. concluded that TAPSE < 20 mm is associated with some degree of either RV or LV dysfunction, and TAPSE > 20 mm suggests normal biventricular systolic function (33). Finally, it has also been shown that TAPSE does not correlate well with RVEF in patients with Tetralogy of Fallot (TOF) (34). Thus, when evaluating right heart strain, low TAPSE values must be added to the entirety of the clinical picture when assessing patients with echocardiography as it relates to diagnostic and prognostic indications.

Among the numerous conditions known to cause right heart strain, TAPSE has been used to evaluate congestive heart failure (CHF) (27), MI (35-37), hypertrophic cardiomyopathy (38), pulmonary hypertension (39-41), post-operatively (42), congenital heart procedures (43), chronic obstructive pulmonary disease (COPD) (44), and PE (23,45-47). In addition, TAPSE has been shown to have prognostic value in many of these conditions, including risk stratification and survival prediction in pulmonary arterial hypertension (PAH) (41,48), heart failure (25,47), LV systolic dysfunction (50), and ARDS (51).

1.3.2 Prognostic Value of RV Dysfunction in Pulmonary Embolism

RV dysfunction is often evaluated by echocardiography in patients with suspected PE. It can aid in particular in both the diagnostic workup and prognostic risk stratification of patients with submassive PE (23,24,45-47,52,53), or massive PE leading to cardiac arrest and pulseless electrical activity (PEA) (54). RV dysfunction has been established as a predictor of increased likelihood of death or

other adverse clinical outcomes from pulmonary embolism (45-47,55). Ribeiro et al. examined 126 consecutive PE-positive patients with 2D echocardiography. They divided patients into two groups: those with normal or slightly reduced RV function, and those with moderately or severely reduced RV function. RV dysfunction was determined by qualitative evaluation of RV free wall motion, qualitative assessment of tricuspid regurgitation (TR), and by quantitative determination of the TR jet using continuous wave Doppler. TR jet analysis was then correlated to right atrial pressure and pulmonary artery systolic pressure using a simplified Bernoulli equation. The two predictors of increased likelihood of in-hospital mortality among the patient population were cancer (hazard ratio of 2.3) and moderate to severe RV systolic dysfunction (hazard ratio of 6.0). They concluded that 2D echocardiography can be useful in risk stratification of patients with RV dysfunction and/or history of malignancy (55).

It has also been shown that point-of-care ultrasound qualitative assessment of RV strain in patients with acute PE in an Emergency Department setting can have prognostic indications. In the first study to examine non-cardiologist-performed RV strain assessment for PE prognosis, Taylor et al. performed a retrospective study of patients with diagnosed PE and had had point of care ultrasound during their course of care in the emergency department. They used RV strain qualitative measures of RV:LV size comparison (≥ 1), RV wall hypokinesis, and McConnell's sign, and adverse clinical outcomes assessed were shock (systolic BP < 100 mmHg refractory to volume loading and requiring vasopressors), respiratory failure requiring intubation, death, recurrent venous thromboembolism, clinical deterioration as

evidenced by transition to higher level of care, and major bleeding. It was determined that RV strain on emergency physician-performed ultrasound was the single most important prognostic factor in adverse hospital events (Odds Ratio = 9.2) (52).

Quantitative 2D echocardiography measures of RV strain have also been shown to have prognostic indication for risk-stratification of patients with acute PE. However, this research has largely been investigated in the field of cardiology. It has been shown that TAPSE is preferable to RV:LV ratio, and other qualitative measures, for risk stratification in initially normotensive patients with acute PE (46). Pruszczyk et al. showed that TAPSE was the only independent predictor of “clinical end-point” (CE), consisting of 30-day PE-related death or thrombolysis. Moreover, normotensive patients with a TAPSE ≤ 15 mm had a hazard ratio of 27.9 and a positive predictive value of 20.9% for CE with a 99% negative predictive value, while a TAPSE ≤ 20 mm had a positive predictive value of 9.2% for CE with a 100% negative predictive value. Therefore, patients with a TAPSE ≤ 15 mm can be identified as high risk for 30 day acute PE-related mortality, while those with a TAPSE > 20 mm can be identified as a very low-risk group (46).

In the Emergency Department setting, little research has been done to evaluate the prognostic value of TAPSE performed by emergency physicians. Zanobetti et al. investigated whether one or more echocardiographic indexes could predict short-term evolution towards RV dysfunction in patients affected by PE, with the goal of tailoring therapy in the first hours after diagnosis according to the hemodynamic profile. They examined sonographic signs of RV dysfunction at the

time of diagnosis with PE (confirmed by CT), 7 days after diagnosis, and 1 month after diagnosis, to determine improvement of RV systolic function over time. In the patient group with low TAPSE (as defined by TAPSE below the mean value of 15 mm), and high pulmonary artery systolic pressure (PASP) (as defined by PASP above the mean value of 62 mmHg), considerable improvement of RV systolic function 7 days after diagnosis/treatment only occurred if the patients received thrombolytic therapy compared to anticoagulation. That is to say, normotensive patients in that category that received Heparin only did not regain RV systolic function within one week of diagnosis and treatment. It was concluded that an intermediate-risk of normotensive patients with depressed TAPSE and elevated PASP may benefit from thrombolytic therapy after the exclusion of bleeding risk (47). While this was the first study regarding the assessment of RV dysfunction using emergency physician-performed echocardiography, the study only examined the prognostic value of echocardiography indices as they relate to the improvement of RV function post PE diagnosis and therapy, not as they relate to adverse clinical outcomes.

1.3.3 Inter-observer Reliability of TAPSE

As previously mentioned, easy and reliable quantitative measures of right heart strain on bedside echo would be an effective tool for emergency physicians for risk stratification of patients with PE. Though qualitative measures can be useful, the inter-observer agreement is not always strong. For example, a retrospective study of patients presenting to the ED with chest pain, dyspnea, or hypotension,

who received a limited bedside echo in the ED and a subsequent consultative echo within 72 hours, showed moderate agreement ($\kappa = 0.44$) for RV dilation (53).

TAPSE has been shown to have good inter-observer reliability across a multitude of cardiac and pulmonary pathologies, including inferior wall MI³³, hypoplastic left heart syndrome⁵⁴, pulmonary hypertension (41,48), and simply correlating TAPSE to tricuspid regurgitation (TR) and RVEF (57). In acute PE of normotensive patients, Kopečna et al. demonstrated that TAPSE had the highest inter-observer reliability ($\kappa = 0.86$) compared to other qualitative measures of RV strain, including that of RV enlargement by diameter ($\kappa = 0.45$) and RV enlargement by RV:LV ratio ($\kappa = 0.65$) (45). However, the inter-observer reliability of TAPSE among emergency physicians has yet to be investigated.

1.4 Electrocardiography in Acute Pulmonary Embolism

1.4.1 Diagnostic and Prognostic Indication: The Daniel Score

While many signs of acute right heart strain can be found with echocardiography, as previously mentioned, as well as the numerous blood tests and CT imaging that can be used to aid in the workup of a patient with undifferentiated dyspnea and suspected PE, there is still a crucial role for electrocardiography (ECG) in the diagnostic and prognostic evaluation of patients with acute PE. ECG is one of the first tests performed in the ED and is rapidly interpretable, low-risk, and inexpensive. When one thinks of the ECG related to PE, one generally thinks of the “textbook” S1Q3T3. However, S1Q3T3 has been found to be relatively insensitive for PE and its prevalence has been found in variable rates among PE positive patients (11% to 52%) (4). Digby et al., reviewed the ECG in the

setting of PE literature, and found that ECG plays a valuable role for prognostication for PE (4). ECG abnormalities were found to be reasonable predictors of hemodynamic decompensation (58), RV dysfunction (59), elevated mean pulmonary arterial pressure (60), in-hospital complication (61,62), cardiogenic shock (63), and mortality (64,65).

As previously mentioned, the pathophysiology of PE may lead to ischemic changes in the right ventricular myocardium due to increased demand. ECG changes may thus reflect depolarization abnormalities (such as in RBBB), or repolarization abnormalities (such as in ST segment elevation, depression, or inverted T waves) (4). ECG abnormalities that may be observed in acute PE, and have been evaluated in the literature include sinus tachycardia, RBBB, T wave inversions, S1Q3T3, ST depression (STD), ST elevation (STE), axis deviation, supraventricular tachycardia, P pulmonale, the QR sign, long QT, QRS fragmentation and Brugada phenocopy (4).

In 2001, Daniel et al. created a comprehensive scoring system for ECG findings in acute PE (66). The scoring system was as follows (with points awarded shown in brackets): sinus tachycardia (2), incomplete RBBB (2), complete RBBB (3), TWI in V1-V4 (0-12 depending on depth), S wave in I (0), Q wave in III (1), TWI in III (1), S1Q3T3 (2). With 21 being the maximum score, a cutoff of 10 was 23.5% sensitive and 97.7% specific for the recognition of severe pulmonary hypertension secondary to PE. They found the derived ECG score increases with the severity of pulmonary hypertension from PE (66).

Though the Daniel Score provided a comprehensive scoring system for diagnosing pulmonary hypertension in patients with suspected PE, it did not yield

prognostic value for the use of risk stratification. Additionally, Digby's review of the literature illustrated that findings not included in the Daniel Score, TWIs in non-precordial leads, STD, STE, the QR sign, QRS fragmentation and atrial fibrillation, yielded prognostic value for patients with acute PE. In particular, it was shown that patients with acute PE and right ventricular dysfunction having ischemic ECG patterns had higher mortality than patients with acute PE and right ventricular dysfunction without ischemic ECG patterns (67).

1.4.2 Correlating Echocardiography and Electrocardiography: TwiST

With the continued expansion of bedside echo in the ED as a diagnostic and prognostic exam for patients with suspected PE, the ability to combine laboratory results, echo findings and ECG findings in risk stratification has dramatically increased. Thus far, one study has examined correlating echo and ECG findings to short-term adverse clinical outcomes in an emergency room setting. In particular, a simplified version of the Daniels Score, the TwiST score, was derived and correlated to RV strain and adverse clinical outcomes (68). Hariharan et al. defined RV strain based on echocardiography, CTPA, or biomarker results. Their echocardiography criteria of RV strain consisted of RV hypokinesis, dilation, and abnormal interventricular septal movement. They derived a 10-point ECG score (TwiST) for risk stratification based on modifying the Daniel Score. The scoring system was as follows (with points awarded shown in brackets): T wave inversions in V1-V3 (5), S wave in lead I (2), sinus tachycardia (3). Adverse clinical outcomes were measured after 5 days (68).

They found that they could effectively risk stratify 85% of patients with acute PE. A TwiST score of ≤ 2 excluded RV strain with 85% sensitivity whereas a score of ≥ 5 was 93% specific for RV strain in patients with PE. Additionally, the same cut-off values were 76% sensitive and 87% specific for 5-day adverse clinical events (68). It should be noted that echoes were performed within 3 days after diagnosis of acute PE, PE negative counterparts were not enrolled, RV strain identified by echocardiography only accounted for 35% of confirmed RV strain in the population, and all echo measurements of RV strain were qualitative in nature. While the study results provide immense value to the emergency physician, they also provide clear indication to further investigate the value of expanding the role of bedside echocardiography in a prospective manner. A quantitative measure of RV strain such as TAPSE, with known prognostic value, that can be correlated to ECG findings and adverse clinical events can be an essential tool in risk stratification of patients with acute PE.

2. Statement of Purpose

In patients with PE, TAPSE has been shown to correlate strongly with other echocardiography measurements of RV function. It has also been shown to predict adverse clinical events. Though the use of TAPSE in assessing patients with suspected PE has been recently reported in the literature, thus far only one study has been published regarding its use by emergency medicine physicians (EMPs). Additionally, no study has analyzed the comparison of electrocardiography scoring assessments for right heart strain to TAPSE in suspected pulmonary embolism. This study aims to examine the diagnostic predictability of the use of TAPSE by EMPs in suspected PE, and the correlation of TAPSE to other established electrocardiographic predictors of right heart strain. Additionally, this study aims to investigate the use of these parameters in predicting clinical outcome of patients with PE.

We hypothesized high Daniels scores (≥ 10) or high TwiST scores (≥ 5) would correlate to having RV systolic dysfunction determined by TAPSE, and that Daniels scores and Twist scores would be higher, while TAPSE scores would be lower, in PE positive patients. We also hypothesized that patients who received PE “elevated care” (PEEC), defined as the need for thrombolysis, pressors, and/or ICU stay ≥ 1 day, would have higher Daniels scores and TwiST scores, and lower TAPSE measurements than those who did not.

This study aims to expand the scope of practice for EMPs and provide a diagnostic tool in evaluating and treating patients presenting with undifferentiated dyspnea.

3. Methods

3.1 Design

We performed this study at the emergency department (ED) of Yale-New Haven Hospital (YNHH), a large, urban, academic hospital that sees more than 80,000 ED visits per year and has an intensive care unit (ICU) admission rate of approximately 15%. The design of the study was a prospective, blinded, observational cohort study of adult (age ≥ 18) ED patients with suspected pulmonary embolism. IRB approval was obtained, and enrollment was nonconsecutive, and based on convenience of ED research staff. Most patients were enrolled between the hours of 7 AM and 8 PM during weekdays during the period of March 2015 to September 2015. Research staff screened patients for who computed tomography pulmonary angiography (CTPA) was ordered by the attending physician. Patients were then approached for eligibility and enrollment with informed consent, and bedside echocardiography was performed as soon as conveniently possible, without delaying standard patient care.

3.2 Eligibility Criteria

Enrollment criteria included any adult patient for whom CTPA was ordered and completed for concern of pulmonary embolism. Board certified radiologists interpreted all radiographic findings as a part of routine clinical care. Patients were excluded from the study if they were under 18, prisoners, wards of the state, or unable to provide informed consent.

3.3 Echocardiography

Subjects underwent transthoracic echocardiography by trained ED providers using a Phillips Sparq Ultrasound System. Five views were obtained using the phased array probe and images were recorded. The views obtained were the parasternal long view, parasternal short view, apical 4 chamber view, subxiphoid view and an inferior vena cava (IVC) view. The following measures were either qualitatively or quantitatively recorded: RV dilation (ratio greater than 1:1 with LV), McConnell's sign, presence of tricuspid regurgitation (TR), velocity of tricuspid regurgitation jet, IVC collapsibility and TAPSE. TR jet velocity was determined using continuous wave Doppler in the apical 4 chamber view. TAPSE was determined using Motion mode (M-mode) over the tricuspid annulus against the RV free wall. Total displacement was measured from end-diastole to end-systole, with the distance being determined by the vertical change from the top of the trough to top of the peak on the wave form seen in M-mode (figure 1). Low TAPSE was determined to be $\leq 17\text{mm}$. Sonographers were blinded to patient CTPA results.

3.4 Electrocardiography

A standard 12-lead ECG was performed in the ED for all but 5 patients enrolled in the study. ECGs were interpreted by a single, research member, who trained in interpreting ECGs for 5 months prior to interpreting the ECGs of enrolled patients in this study. The ECGs were assessed and scored for Daniels Criteria: sinus tachycardia (2), incomplete RBBB (2), complete RBBB (3), TWI in V1-V4 (0-12 depending on depth), S wave in I (0), Q wave in III (1), TWI in III (1), S1Q3T3 (2), for a possible total of 21 points. ECGs were also assessed and scored for TwiST Criteria:

T wave inversions in V1-V3 (5), S wave in lead I (2), sinus tachycardia (3), for a possible total of 10 points. The ECG reader was blinded to patient outcome and TAPSE measurement while reviewing and scoring ECGs. Figure 2 shows an example of a patient who was PE positive and had high Daniels and TwiST scores of 20 and 10 respectively.

3.5 Prognostic Evaluation: PE Elevated Care (PEEC)

Patients diagnosed with pulmonary embolism were followed for up to 30 days as inpatients and using death registries to determine any association between findings on ECG and bedside echo to morbidity, mortality, and level of care required. These included factors such as disposition (ICU, step-down unit, floor), requirement of pressors, requirement of thrombolysis, length of stay and mortality. In addition, we stratified patients with these indicators into PE positive patients that required PE Elevated Care (PEEC), defined as the need for thrombolysis, pressors, and/or ICU stay ≥ 1 day, and patients who did not require PEEC.

3.6 Statistical Analysis

3.6.1 Diagnosis of PE

Diagnostic characteristics of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and positive and negative predictive values, were determined for diagnosing patients with PE using the Daniels score, TwiST score, and 2 different TAPSE values. One TAPSE value of 17 mm was used for higher specificity, and a value of 21 mm was used for higher sensitivity. Statistical analyses were calculated using the online software VassarStats (vassarstats.net).

3.6.2 Comparison of TAPSE and ECG

Diagnostic characteristics of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and positive and negative predictive values were determined for the Daniels and TwiST scores ability to diagnose right heart strain as determined by a “low TAPSE” of ≤ 17 mm. Statistical analyses were calculated using the online software VassarStats (vassarstats.net).

Additionally, patients were stratified into “low TAPSE” and “normal TAPSE” groups. Mean ECG scores for the Daniels and TwiST criteria were compared between groups using student’s t-test. Patients were also stratified into PE positive and PE negative groups. Mean TAPSE measurements, and Daniels score and TwiST scores were compared between groups using student’s t-test. Statistical analyses were calculated using the online software VassarStats (vassarstats.net).

3.6.3 TAPSE, ECG and PEEC

Mean TAPSE, Daniels and TwiST scores and relative risks were calculated for patients who received “elevated care” compared to those who did not. The relative risk of low TAPSE (≤ 17 mm) and high Daniels (≥ 10) and TwiST (≥ 5) for elevated care were also compared. Statistical analyses were calculated using the online software VassarStats (vassarstats.net).

3.6.4 The Role of Research Study Members

In regards to the methods described above, I enrolled 90 of the 110 patients in the research study and performed their echocardiogram in the emergency department. Additionally, I interpreted all of the ECGs for the study population as well as performed all statistical analyses. Patients were also enrolled by Dr. James

Daley, Dr. Michael Kennedy Hall, Dr. Joseph Pare, Dr. Rachel Liu, Dr. Andrew Taylor and Dr. Chris Moore.

4. Results

4.1 Enrollment Demographics and Hospital Course

We enrolled 110 patients in total, 45 men and 65 women, and 23 patients were diagnosed with a pulmonary embolism (PE positive). Of the 23 patients with PE, 13 were men and 10 were women. Of the 110 patients enrolled, 105 had recorded ECG's, and all underwent bedside echocardiography. Enrolled patients ranged from 18 to 90 years old, with an average age of 58.6 (SD±17.4) years old. PE positive patients had an average age of 63.4 (SD±15.1) years old, while PE negative patients had an average age of 57.4 (SD±17.9) years old. 23 patients were discharged from the Emergency Department (1 who was PE positive), 30 patients were admitted to the floor (13 who were PE positive) and 24 were admitted to either the step down unit (SDU) or intensive care unit (ICU) (9 who were PE positive) (Table 1). Other dispositions of patients that were not tracked include telemetry observation and admission to the chest pain center. The mean length of stay for enrolled patients was 3.9 (SD±5.4) days. The mean length of stay for PE positive patients was 6.7 (SD±6) days, while the mean length of stay for PE negative patients was 3.3 (SD±5.1) days (Table 1).

4.2 Diagnosis of PE

When total Daniels score was evaluated for the ability to diagnose PE, we first began with the ability of a low Daniels score (≤ 2) to rule out a PE, that is, the ability to “diagnose” PE negative. A Daniels score of ≤ 2 was 58% (95% CI, 46%-

58%) sensitive and 50% (95% CI, 28%-72%) specific for determining PE negative patients. In addition, it had a positive likelihood ratio of 1.2, a negative likelihood ratio of 0.87, a positive predictive value of 83% and a negative predictive value of 22% (Table 2). Then, the ability of the Daniels score to predict PE was evaluated in an increasing fashion, beginning with Daniels score of ≥ 3 , followed by cutoffs of 7, 10, 12 and 17. Sensitivities decreased from 50% (95% CI 28%-72%) to 13% (95% CI 2%-42%) among these groups, while specificities increased from 58% (95% CI 46%-68%) to 99% (95% CI 93%-100%) (Table 2). Positive likelihood ratios increased from 1.2 (0.7-1.95) to 12 (1.2-124), while negative likelihood ratios showed varying ranges among cutoff values (Table 2). Positive predictive values increased from 22% (11%-37%) to 67% (13%-98%) and negative predictive values increased from 83% (71%-91%) to 87% (79%-93%) (Table 2).

When total TwiST score was evaluated for the ability to diagnose PE, similar to with the Daniels score, we first began with the ability of a low TwiST score (≤ 2) to rule out a PE, that is, the ability to “diagnose” PE negative. A TwiST score of ≤ 2 was 63% (95% CI, 52%-73%) sensitive and 50% (95% CI, 27%-73%) specific for determining PE negative patients. In addition, it had a positive likelihood ratio of 1.4, a negative likelihood ratio of 0.79, a positive predictive value of 86% and a negative predictive value of 22% (Table 3). The ability of the TwiST score to predict PE was evaluated in an increasing fashion, beginning with TwiST score of ≥ 3 , followed by cutoffs of 5, 7, and 8. Sensitivities decreased from 50% (95% CI 27%-73%) to 29% (95% CI 12%-52%) among these groups, while specificities increased from 63% (95% CI 52%-73%) to 93% (95% CI 85%-97%) (Table 3). Positive

likelihood ratios increased from 1.4 (0.8-2.3) to 4 (1.4-11), while negative likelihood ratios showed varying ranges among cutoff values (Table 3). Positive predictive values increased from 22% (11%-38%) to 50% (22%-78%) and negative predictive values decreased from 86% (74%-93%) to 84% (74%-90%) (Table 3).

With regard to the ability of TAPSE to diagnose PE, TAPSE values ≤ 17 mm were 57% (95% CI 34%-77%) sensitive and 87% (95% CI 78%-93%) specific in diagnosing PE (Table 4). Additionally, the cutoff of ≤ 17 mm had a positive likelihood ratio of 4.3 (2.2-8.3) and a negative likelihood ratio of 0.5 (0.3-0.8), as well as a positive predictive value of 54% (33%-74%) and a negative predictive value of 88% (79%-94%). TAPSE values ≤ 21 mm were 79% (95% CI 57%-92%) sensitive and 67% (95% CI 55%-76%) specific in diagnosing PE. Additionally, the cutoff of ≤ 21 mm had a positive likelihood ratio of 2.4 (1.6-3.4) and a negative likelihood ratio of 0.31 (0.14-0.69), as well as a positive predictive value of 40% (27%-56%) and a negative predictive value of 92% (81%-97%) (Table 4).

4.3 Comparison of ECG Scoring and TAPSE Measurements

In evaluating a correlation between higher Daniels and TwiST scores and lower TAPSE scores, the ability of Daniels and TwiST scores to “diagnose” a low TAPSE (≤ 17 mm) was determined. Similarly, in the evaluation of diagnosing PE, a Daniels score of ≤ 2 was evaluated to rule out a low TAPSE. A Daniels score of ≤ 2 was 60% (95% CI, 48%-71%) sensitive and 77% (95% CI, 55%-92%) specific for determining high TAPSE patients. In addition, it had a positive likelihood ratio of 2.64, a negative likelihood ratio of 0.5, a positive predictive value of 91% and a negative predictive value of 35% (Table 5). Then, the ability of the Daniels score to

predict low TAPSE was evaluated in an increasing fashion, beginning with Daniels score of ≥ 3 , followed by cutoffs of 7, 10, 12 and 17. Sensitivities decreased from 77% (95% CI 55%-92%) to 13% (95% CI 3%-34%) among these groups, while specificities increased from 60% (95% CI 48%-71%) to 100% (95% CI 95%-100%) (Table 5). Positive likelihood ratios increased from 2.64 (1.2-5.8) to 17 (2-140), while negative likelihood ratios showed varying ranges among cutoff values (Table 5). Positive predictive values increased from 35% (22%-50%) to 100% (29%-100%) and negative predictive values decreased from 91% (71%-97%) to 80% (70%-87%) (Table 5).

A TwiST score of ≤ 2 was 70% (95% CI, 68%-79%) sensitive and 87% (95% CI, 66%-97%) specific for determining high TAPSE patients. In addition, it had a positive likelihood ratio of 5.34, a negative likelihood ratio of 0.35, a positive predictive value of 95% and a negative predictive value of 45% (Table 6). The ability of the TwiST score to predict low TAPSE was also evaluated in an increasing fashion, beginning with a TwiST score of ≥ 3 , followed by cutoffs of 5, 7, and 8. Sensitivities decreased from 70% (95% CI 68%-79%) to 39% (95% CI 20%-61%) among these groups, while specificities increased from 70% (95% CI 68%-79%) to 96% (95% CI 89%-99%) (Table 6). Positive likelihood ratios increased from 5.34 (2-15) to 10.3 (3-35), while negative likelihood ratios showed varying ranges among cutoff values (table 6). Positive predictive values increased from 45% (30%-62%) to 75% (43%-95%) and negative predictive values decreased from 95% (86%-99%) to 84% (75%-91%) (Table 6).

Patients with low TAPSE had a mean Daniels score of 7.26 (SD±5.9) while patients with a TAPSE > 17 mm had a mean Daniels score of 2.5 (SD±2.5). Patients with low TAPSE had a mean TwiST score of 5.52 (SD±3.3) while patients with a TAPSE > 17 mm had a mean TwiST score of 1.79 (SD±2.4). Mean Daniels scores and TwiST scores were significantly different between low and high TAPSE groups ($p<0.0001$), and high Daniels and TwiST scores correlated to low TAPSE ($p<0.0001$ and $p=0.0002$ respectively). PE positive (PE+) patients had a significantly lower mean TAPSE value of 17.6 mm (SD±5.0) compared to 22.2 mm (SD±5.3) in PE negative (PE-) patients ($p=0.0003$). PE+ patients had a significantly higher mean Daniels score of 5.95 (SD±6.05) compared to 2.96 (SD±3.24) in PE- patients ($p=0.0024$). PE+ patients had a significantly higher TwiST score of 4.38 (SD±3.46) compared to 2.24 (SD±2.77) in PE- patients ($p=0.0033$) (Table 7).

4.4 PEEC v. Non-PEEC

Mean TAPSE for patients requiring PEEC was 15.2 mm (SD±5.07) compared to 19.4 mm (SD±4.27) for those who did not ($p=0.047$). Mean Daniels score for patients requiring PEEC was 8.2 (SD±5.4) compared to 3.9 (SD±6.1) for those who did not ($p=0.11$). Mean TwiST for patients requiring PEEC was 6.6 (SD±3.5) compared to 3.0 (SD±2.96) for those who did not ($p=0.020$). TAPSE ≤17 mm, Daniels ≥10, and TwiST ≥5 had increased risks of 6.9 ($p=0.045$), 2.0 ($p=0.11$) and 4.4 ($p=0.025$) respectively for requiring PEEC (Table 8).

5. Discussion

In the context of using echocardiography and electrocardiography to aid in the diagnosis of PE in suspected patients, it was found that high Daniels and TwiST

scores were specific for diagnosing PE in this patient population. A Daniels score ≥ 10 and a TwiST score ≥ 7 were 94% and 90% specific for PE respectively. Though this study had a relatively small enrollment, and specifically, a small number of PE positive patients, the trends in increasing specificity with increasing TwiST and Daniels score may relate to their ability to detect right heart strain in PE positive patients. This finding correlates well with the prior literature regarding the Daniels and TwiST scores. As Daniels found that an increase in his derived ECG score corresponded to increasing severity of pulmonary hypertension from PE (66), and Hariharan et al. showed that the TwiST score effectively risk stratified 85% of patients with acute PE (68), it is reasonable to conclude that higher Daniels scores and TwiST scores in a patient population with suspected pulmonary embolism would aid in detection of RHS in those with acute pulmonary embolism.

When analyzing the utility of TAPSE in diagnosing PE, the cutoff of 17 mm yielded a higher specificity for PE, however the sensitivity was low. The sensitivity was increased to 79% when 21 mm was used as a cutoff, however this decreased the specificity to 67%. This may be indicative of the utility of differing ranges of TAPSE values that likely correspond to the degree of RHS. It may be useful to have separate cutoff values as seen in this study to maximize sensitivity and specificity. That is, a TAPSE less than 17 mm may be useful for ruling in PE, while a TAPSE greater than 21 mm may be useful at ruling out PE. An “intermediate zone” between 17 and 21 mm may exist in which clinical judgement and further testing would be useful. That said, this study only examined those cutoffs at 17 mm and 21 mm. Further research with a larger population would be beneficial in order to determine

the best values to optimize sensitivity and specificity in diagnosing PE in patients with suspected PE. These cutoff values, however, are consistent with prior literature in the use of TAPSE as a diagnostic tool for RV dysfunction. An optimal cutoff for diagnosing RV dysfunction using TAPSE has been suggested to be < 17.5 mm (31), while an optimal cutoff for concluding normal biventricular function has been suggested to be > 20 mm (33).

When stratifying PE positive and PE negative patients, it was determined that PE positive patients had significantly lower TAPSE measurements, as well as significantly higher Daniels and TwiST scores. It should be emphasized that the patients in this study were all suspected of having a PE to the point at which the attending physician ordered a CTA/PE protocol. Thus, it is important to keep in mind that these diagnostic tools certainly cannot make a diagnosis of PE alone, but rather can be used in the context of a patient with suspected PE to rule in or out evidence of right heart strain. This is to say, among any patient, these tools likely have low sensitivity and specificity for diagnosing PE, but are likely useful in diagnosing right heart strain. In a patient with evidence of right heart strain either by Daniels score or TwiST score, by TAPSE measurement, or by some combination, for whom PE is on the differential, these tools may help aid in the work up or diagnosis of PE.

Additionally, it was shown that increasing Daniels and TwiST scores correlate well to RHS as defined by low TAPSE. When correlating Daniels and TwiST scores to measured TAPSE values, lower Daniels and TwiST scores had higher sensitivities of ruling out a low TAPSE while higher Daniels and TwiST scores were

more specific for ruling in a low TAPSE. Though this was expected as all of these modalities have been linked to right heart strain, it was encouraging to find that trends existed, as TAPSE is more a measure of dynamic function than what may conventionally be used to diagnose right heart strain (RV>LV on CT or echo). Additionally, it appears as though the TwiST score provided better sensitivity and the Daniels score provided better specificity in diagnosing RV dysfunction as indicated by low TAPSE. This is likely due to the nature of the two scoring systems, with the Daniels score being far more comprehensive than the TwiST. With only 3 items, it seems the TwiST score has the most pertinent elements to rule out right heart strain, that is, tachycardia, strain on the RV conduction system as evidenced by an S wave in lead I, and ischemic changes as evidenced by T-wave inversion in precordial leads V₁-V₃. A TwiST score <3 was 87% sensitive in ruling out a low TAPSE compared to 77% using the Daniels score. With regard to specificity, due to the comprehensiveness of the Daniels score, it had increased specificity for ruling in low TAPSE values. Both a Daniels score of ≥10, and a TwiST score of ≥8 had specificities of 96%. However, because the Daniels score is more inclusive and has many different iterations of point totals, specificity was able to be increased to 99% and 100% for scores ≥12 and ≥17 respectively. When stratifying patients into low TAPSE values (≤17 mm) and high TAPSE values, patients with low TAPSE values had significantly higher mean Daniels and TwiST scores. This finding corroborates the value of TAPSE as a marker for RV systolic function, as well as the ECG scoring criteria as being predictive of RV strain. Moreover, we found additional corroboration with mean Daniels and TwiST scores when stratifying patients into

low and high TAPSE groups, and then PE positive and PE negative groups. Mean Daniels and TwiST scores were significantly higher in the low TAPSE group, and significantly higher in the PE positive group. Additionally, mean TAPSE values were significantly lower in the PE positive group compared to the PE negative group. Again, this highlights the utility of ECG scoring and TAPSE in detecting RHS non-invasively. This intuitively makes sense for patients with suspected PE in that in order to have a suspicion of PE as a diagnosis, the patients are likely symptomatic. The clot burden that produces such symptoms is also responsible for the effect on resistance in the pulmonary circulation. In turn, increased right sided pressures along with supply/demand mismatch likely has a correlating effect on the conduction system. This combination of factors would explain the correlation of PE and RHS with the ECG and echo findings. While this may not be diagnostically useful, it helps illustrate the pathophysiology of PE, and the associated effects on hemodynamics and cardiac conduction and contractility, in particular with the right ventricle.

The findings surrounding prognosis of PE positive patients with regard to the level of care required also seems to correlate with the degree to which the clot affected RV function as determined by TAPSE or ECG scores. Patients requiring “elevated care” had significantly lower TAPSE and significantly higher TwiST. In addition, patients with low TAPSE and TwiST ≥ 5 had significantly increased relative risk of requiring “elevated care.” Physiologically, this makes sense, as these patients have evidence of increased hemodynamic compromise, and it has already been shown that RV dysfunction in PE predicts in-hospital mortality (55). This suggests

that those two point-of-care tests have prognostic value in PE care. However, patient disposition may be subjective, and hospital length of stays often include complications unrelated to the admitting diagnosis. One of the limitations of this study is that more information was not gathered regarding the hospital course of PE positive patients. Additionally, there was no follow up done with regard to long term sequelae or morbidity/mortality and any association with lower TAPSE or high Daniels or TwiST scores on initial presentation. These limitations certainly have implications regarding the findings of this study and their internal validity. We cannot say with certainty that all cases of patients requiring longer hospital stays were directly related to acute pulmonary embolism. Additionally, though we may be able to comment on the short term prognosis and level of care regarding these patients, without long term follow up, we cannot comment on how risk stratification and treatment may affect long term morbidity and mortality.

In conclusion, the results of this study demonstrate a link between TAPSE and ECG scores as determined by the Daniels and TwiST criteria, with RHS being the likely common denominator. Though this may seem inherent based on previous research, this still may provide utility. Hospital resources often differ, and TAPSE is not a measurement that is often taken during bedside echo in emergency departments. Having an understanding that there is a correlation between ECG scoring and TAPSE values will allow practitioners to potentially use either, or both, in evaluating a patient with suspected PE. Additionally, there was correlation with the level of care required, again with RHS/RV dysfunction being the likely common denominator. This is consistent with prognostic data in prior studies, and bedside

echo and/or ECG scoring systems can provide physicians additional information to risk stratify patients with submassive PE who may require a higher level of inpatient care. Of course, this particular study was limited by many factors, notably the small sample and small number of PE positive patients, as well as the fact that it was a convenience sample as opposed to consecutive enrollment, which may have affected the study's internal validity. Additionally, limited data was acquired with regard to patients after their admission to the hospital. Further research would be helpful in further determining the role of using TAPSE and/or the Daniels or TwiST score in diagnosing and prognosticating patients with acute PE. Thus far these modalities have shown to correlate well with RHS, and suggest to have utility in diagnosing PE in a symptomatic patient in which PE is suspected, but confirmatory studies with larger sample sizes would provide more optimal cutoff ranges in adding to the current tools for PE diagnosis and prognosis.

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6. Figures

Figure 1: TAPSE measurement using M-mode over the tricuspid annulus.

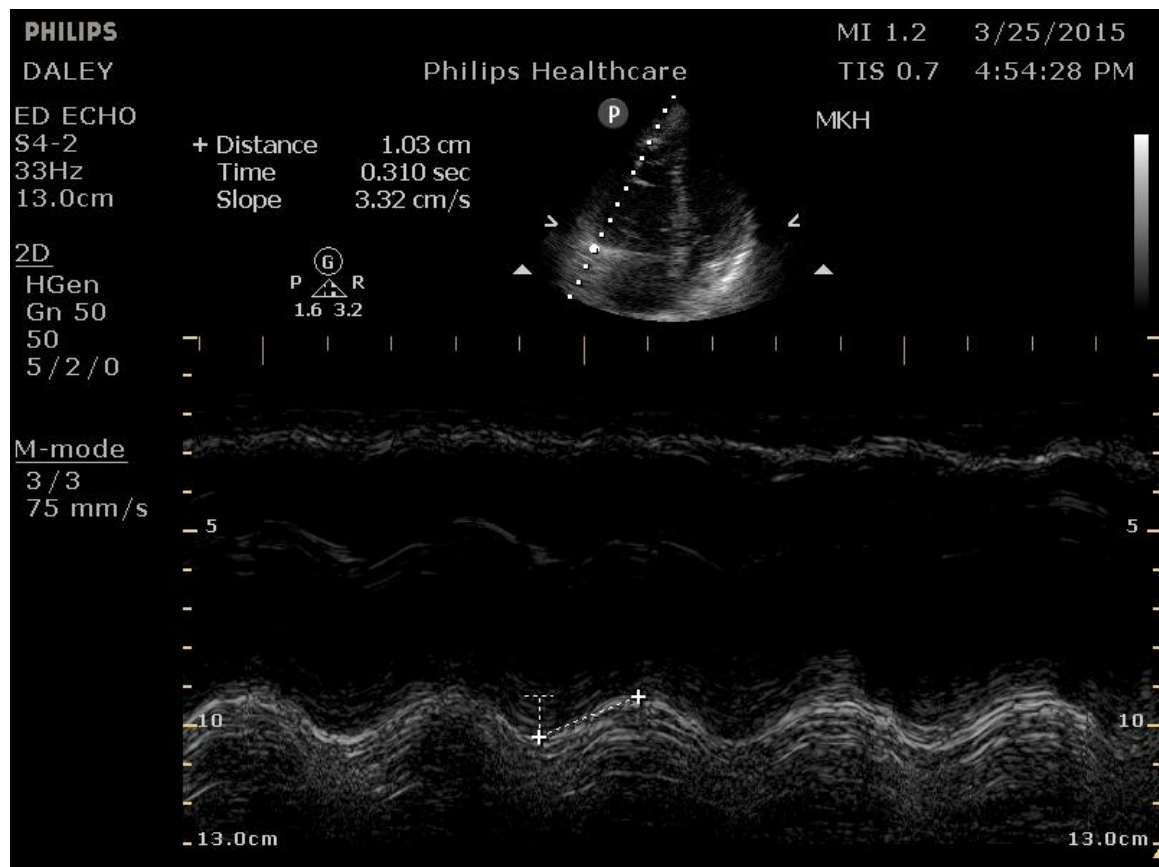
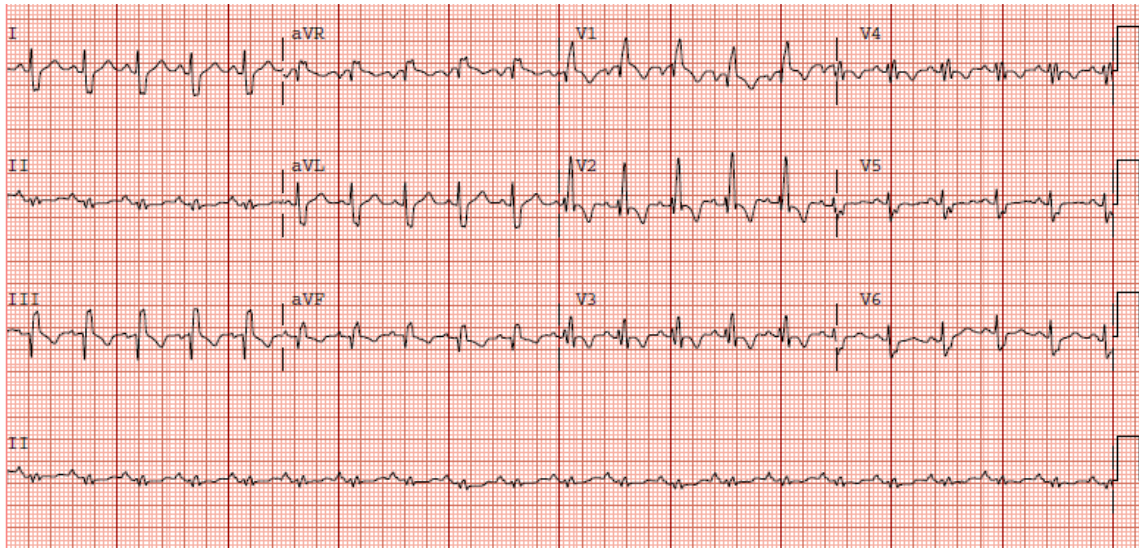


Figure 2: 12-lead ECG tracing of a PE positive patient with a Daniels score of 20 and TwiST score of 10. (Daniels: tachycardia (2), incomplete RBBB (2), TWI V1-V4 (4), TWI in V1 >2mm (2), TWI in V2 >2 mm (3), TWI in V3 >2mm (3), Q III (1), TWI III (1), SIQIIIITIII (2)) (TwiST: TWI V1-V3 (5), SI (2), tachycardia (3))



7. Tables

Table 1: Demographics, dispositions and length of stays for enrolled patients.

	All Subjects (n=110)	PE + (n=23)	PE- (n=87)
Age (\pm SD)	58.6 (\pm 17.4)	63.4 (\pm 15.1)	57.4 (\pm 17.9)
Male (%)	45 (41)	13 (56.5)	32 (36.8)
Female (%)	65 (59)	10 (43.5)	55 (63.2)
Discharged (%)	23 (21)	1 (4.3)	22 (25.2)
Admit to Floor (%)	30 (27)	13 (56.5)	27 (31)
Admit to SDU/ICU	24 (21.8)	9 (39.1)	15 (17)
Length of Stay (\pm SD)	3.9 (5.4)	6.7 (6)	3.3 (5.1)

Table 2: Diagnostic characteristics of Daniels scores in diagnosing PE.

Daniels Score	N(%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Likelihood (95% CI)	Negative Likelihood (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
≤ 2 PE-	59 (56)	58 (46-58)	50 (28-72)	1.2 (0.7-1.95)	0.87 (0.55-1.37)	83 (71-91)	22 (11-37)
≥3	46 (44)	50 (28-72)	58 (46-68)	1.2 (0.7-1.95)	0.87 (0.55-1.37)	22 (11-37)	83 (71-91)
≥7	17 (16)	40 (20-64)	89 (80-95)	3.8 (1.7-8.6)	0.67 (0.47-0.96)	47 (24-71)	86 (77-92)
≥10	12 (11)	33 (15-57)	94 (78-98)	5.6 (2-16)	0.7 (0.5-1)	58 (23-85)	85 (76-92)
≥12	6 (6)	24 (8-50)	98 (91-100)	10.4 (2-52)	0.78 (0.6-1.0)	67 (24-94)	87 (78-93)
≥17	3 (3)	13 (2-42)	99 (93-100)	12 (1.2-124)	0.88 (0.72-1.1)	67 (13-98)	87 (79-93)

Table 3: Diagnostic characteristics of TwiST scores in diagnosing PE.

Twist Score	N(%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Likelihood (0.8-2.3)	Negative Likelihood (0.49-1.3)	PPV, % (95% CI)	NPV, % (95% CI)
≤ 2 PE-	64 (61)	63 (52-73)	50 (27-73)	1.4 (0.8-2.3)	0.79 (0.49-1.3)	86 (74-93)	22 (11-38)
≥3	41 (39)	50 (27-73)	63 (52-73)	1.4 (0.8-2.3)	0.79 (0.49-1.3)	22 (11-38)	86 (74-93)
≥5	20 (19)	43 (23-66)	87 (78-93)	3.3 (1.6-6.9)	0.66 (0.45-1)	45 (23-68)	86 (77-92)
≥7	15 (14)	33 (15-57)	90 (82-96)	3.5 (1.4-8.6)	0.74 (0.54-1.0)	47 (22-73)	84 (75-91)
≥8	12 (11)	29 (12-52)	93 (85-97)	4 (1.4-11)	0.77 (0.59-1.0)	50 (22-78)	84 (74-90)

Table 4: Diagnostic characteristics of TAPSE values in diagnosing PE.

TAPSE (mm)	N(%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Likelihood (2.2-8.3)	Negative Likelihood (0.3-0.8)	PPV, % (95% CI)	NPV, % (95% CI)
TAPSE (17)	24 (22)	57 (34-77)	87 (78-93)	4.3 (2.2-8.3)	0.5 (0.3-0.8)	54 (33-74)	88 (79-94)
TAPSE (21)	47 (44)	79 (57-92)	67 (55-76)	2.4 (1.6-3.4)	0.31 (0.14-0.69)	40 (27-56)	92 (81-97)

Table 5: Diagnostic characteristics of Daniels scores in diagnosing right heart strain as determined by “low TAPSE.”

Daniels Score	N(%)	Sensitivity % (95% CI)	Specificity, % (95% CI)	Positive Likelihood	Negative Likelihood	PPV, % (95% CI)	NPV, % (95% CI)
≤ 2 high TAPSE	53 (52)	60 (48-71)	77 (55-92)	2.64 (1.2-5.8)	0.5 (0.4-0.7)	91 (79-97)	35 (22-50)
≥3	49 (48)	77 (55-92)	60 (48-71)	2.64 (1.2-5.8)	0.5 (0.4-0.7)	35 (22-50)	91 (79-97)
≥7	16(16)	48 (27-69)	92 (84-97)	6.54 (3-16)	0.6 (0.4-0.8)	65 (38-86)	86 (77-92)
≥10	17 (17)	45 (24-68)	96 (89-99)	12.6 (4-42)	0.6 (0.4-0.8)	77 (46-95)	87 (78-93)
≥12	6 (6)	22 (7-44)	99 (93-100)	17 (2-140)	0.8 (0.6-1)	83 (36-100)	81 (72-88)
≥17	3 (3)	13 (3-34)	100 (95-100)	-----	0.9 (0.7-1.0)	100 (29-100)	80 (70-87)

Table 6: Diagnostic characteristics of TwiST scores in diagnosing right heart strain as determined by “low TAPSE.”

TwiST Score	N(%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Likelihood (2-15)	Negative Likelihood (0.24-0.51)	PPV, % (95% CI)	NPV, % (95% CI)
≤ 2 high TAPSE	58 (57)	70 (68-79)	87 (66-97)	5.34 (2-15)	0.35 (0.24-0.51)	95 (86-99)	45 (30-61)
≥3	44 (43)	87 (66-97)	70 (68-79)	5.34 (2-15)	0.35 (0.24-0.51)	45 (30-61)	95 (86-99)
≥5	25 (25)	59 (36-79)	85 (75-92)	3.9 (2.1-7.37)	0.48 (0.29-0.8)	52 (31-72)	88 (79-95)
≥7	15 (15)	45 (24-68)	94 (86-98)	7.27 (3-19)	0.58 (0.4-0.86)	67 (38-88)	86 (77-93)
≥8	12 (12)	39 (20-61)	96 (89-99)	10.3 (3-35)	0.63 (0.45-0.88)	75 (43-95)	84 (75-91)

Table 7: Differences in mean ECG scores for low vs. high TAPSE and PE positive vs. PE negative patients.

	Daniels	Twist	
TAPSE ≤ 17 mm Mean (\pm SD)	7.2 (± 5.9)	5.5 (± 3.3)	
TAPSE > 17 mm Mean (\pm SD)	2.5 (± 2.5)	1.8 (± 2.4)	
Difference (95% CI)	4.7 (3.1-6.4)	3.7 (2.5-5)	
Level of significance	p<0.0001	p<0.0001	
	Daniels	Twist	TAPSE
PE + Mean (\pm SD)	5.9 (± 6.1)	4.4 (± 3.4)	17 mm (± 5.0)
PE - Mean (\pm SD)	2.9 (± 3.2)	2.2 (± 2.7)	22 mm (± 5.3)
Difference (95% CI)	3.0 (1.1-4.9)	2.1 (0.73-3.5)	4.6 (2.2-7.1)
Level of significance	p = 0.0024	p = 0.0033	p = 0.0003

Table 8: Mean TAPSE and ECG scores for PEEC vs. non-PEEC patients, and relative risk of PEEC.

	TAPSE	Daniels	Twist
PEEC Mean (\pm SD)	15 mm (5.1)	8.2 (5.4)	6.6 (3.5)
Non-PEEC Mean (\pm SD)	19 mm (4.2)	3.9 (6.1)	3.0 (2.9)
Difference (95% CI)	4.1 (0-8.2)	4.3 (-1.0 to 9.6)	3.6 (0.64-0.65)
Level of significance	p = 0.047	p = 0.11	p = 0.020
	TAPSE ≤ 17 mm	Daniels ≥ 10	Twist ≥ 5
Relative Risk of elevated care	6.9	2.0	4.4
95% CI	1-46	0.86-4.6	1.2-16
Level of significance	p = 0.045	p = 0.11	p = 0.025