Echocardiographic Predictors of Long-Term Mortality in Patients Presenting With Acute Pulmonary Embolism

Andrew D Terluk, MBBS[a,b,c,1], Siddharth J Trivedi, BSc, BMedSci, MBBS[b,d,1], Leonard Kritharides, PhD[e], Vincent Chow, BSc, MBBS, PhD[e], Ee-May Chia, MBBS, BSc, MPH[f,g], Karen Byth, PhD[b,h], Christian J Mussap, BSc, MBBS, PhD[a,g], Austin C.C. Ng, MBBS, BSc, MMed[e], and Liza Thomas, MBBS, PhD[b,d,g,*]

Pulmonary embolism (PE) is associated with a high mortality; whether echocardiographic evaluation at presentation predicts long-term adverse outcomes is of importance. We sought to determine if a composite of routinely obtained echocardiographic parameters could determine long-term adverse events in PE patients. Right ventricular (RV) size and function and right atrial (RA) size were retrospectively evaluated in 233 consecutive PE patients with an inpatient echocardiogram, and compared with 70 healthy controls; mortality at 3 years was confirmed. PE patients had increased RV size (RV parasternal long-axis diameter [RVPLAX] and RV end-diastolic volume [$p < 0.001$ for both]) and RA area ($p < 0.001$). RV function was reduced in PE patients (RV fractional area change and RV ejection fraction [$p < 0.001$ for both]). Peak tricuspid regurgitation (TR) velocity was higher in the PE group. At follow-up (3.0 ± 2.1 years), 61 patients died; multivariable analysis demonstrated RVPLAX diameter >37 mm (hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.3 to 4.2; $p = 0.005$), RA area >20 cm^2 (HR 2.0, 95% CI 1.1 to 3.5; $p = 0.016$), and TR velocity >2.9 ms^{-1} (HR 1.9, 95% CI 1.1 to 3.4; $p = 0.021$), were independent echocardiographic predictors of mortality. Patients with all 3 "risk markers" had ~17-fold increased mortality compared with those with no "risk markers" (HR 16.9, 95% CI 6.1 to 47.2; $p < 0.001$). In conclusion, a composite of routinely collected echocardiographic parameters, namely an enlarged RA and RV (RVPLAX diameter), and TR velocity, were independent predictors of mortality in PE patients, with an exponential increase in mortality when all 3 parameters were significantly altered. Prospective validation is required to confirm these preliminary observations. **(Am J Cardiol 2019;124:285−291)**

Acute pulmonary embolism (PE) is the third most common diagnosis in cardiovascular disease.[1] Rates of PE have been increasing,[2] with an associated significant mortality risk, with a PE registry reporting a >10% short-term mortality at 30 days.[3] Although a transthoracic echocardiogram (TTE) can aid in the diagnosis of PE, its use in confirmed PE is currently recommended in guidelines to risk stratify intermediate risk patients.[4,5] There are several reports on echocardiographic determinants of acute outcome at 30 days following PE[6,7]; however, there is a paucity of data on predictors of long-term outcome. Right ventricular (RV) enlargement and dysfunction in PE portends a worse prognosis[8,9]; however, it remains unclear as to which TTE parameters provide utility in stratifying long-term risk.[10] Risk stratification is of particular relevance in submassive PE where in-hospital mortality approaches 15% despite a normal blood pressure.[11] With the development of emergent interventional and thrombolytic therapies,[12] risk stratification of patients diagnosed with PE is increasingly important, as this could aid in choice of therapy. We sought to determine if a composite of simple, routinely evaluated echocardiographic parameters at index hospital admission are useful for long-term risk stratification in PE patients.

Methods

The study population comprised consecutive PE patients (January 2001 to December 2010) at 2 tertiary institutions (Liverpool Hospital and Concord Hospital, Sydney, Australia) who had a TTE during admission. Patients were identified retrospectively from medical records; inclusion required documented clinical diagnosis with treatment of acute PE, with prespecified imaging diagnostic criteria (i.e., intermediate-high probability ventilation-perfusion scintigraphy (V/Q scan) or computed-tomography pulmonary angiogram

[a]Department of Cardiology, Liverpool Hospital, Sydney, Australia; [b]Westmead Clinical School, University of Sydney, Sydney, Australia; [c]Sydney Adventist Hospital Clinical School, University of Sydney, Sydney, Australia; [d]Department of Cardiology, Westmead Hospital, Sydney, Australia; [e]Department of Cardiology, Concord Hospital, University of Sydney, Sydney, Australia; [f]Department of Cardiology, St George Hospital, Sydney, Australia; [g]South West Clinical School, University of New South Wales, Sydney, Australia; and [h]Research and Education Network, Western Sydney Local Health District, Sydney, Australia. Manuscript received January 21, 2019; revised manuscript received and accepted April 5, 2019.

Authors contribution: Andrew Terluk and Siddharth Trivedi are equal first authors. All authors contributed to the design, data collection, and analysis and manuscript preparation.

[1]Equal first authors.

See page 290 for disclosure information.

*Corresponding author: Phone: +61 2 8890 8140; fax: +61 2 8890 8323.

E-mail addresses: liza.thomas@sydney.edu.au; l.thomas@unsw.edu.au (L. Thomas).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.04.039

[CTPA] showing thrombus). For patients presenting with recurrent PE, only the initial presentation was included.

We did not risk-stratify patients on the basis of previously established clinical indices,[11,13] as the study aim was to evaluate the prognostic utility of echocardiography. Healthy subjects with no previous history of malignancy, cardiovascular or respiratory illness, not on cardiac or respiratory medications, whose TTEs were available from a departmental database, served as controls. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Human Research Ethics Committee of both institutions.

Patient demographics and clinical characteristics were collected from hospital and local doctor medical records, as previously described.[10,14] This included the imaging investigation used to diagnose PE, risk factors for PE, and in-hospital outcomes. A history of cardiovascular disease (ischemic heart disease, cardiac failure, valvular heart disease, atrial fibrillation/flutter, peripheral vascular disease, stroke), cardiac risk factors (hypertension, hyperlipidemia, diabetes, current or ex-smoker), malignancy, pulmonary disease (asthma, emphysema), neurodegenerative disease (dementia, Parkinson's disease), and chronic renal disease, based on the *International Classification of Disease, Tenth Revision (ICD-10)*, were recorded.

The cohort were tracked for mortality events using a state-wide death registry. A censor date was predetermined to allow a minimum follow-up of 3 years. Adverse events were corroborated with hospital electronic medical records. Two hundred and thirty-nine PE patients underwent a TTE at a mean of 3.4 days after admission to hospital; TTEs are routinely performed using a standardized protocol at both centers. All TTEs were independently reviewed by an experienced cardiologist, blinded to patient details. Six patients were excluded before analysis due to suboptimal and limited images.

Echocardiograms were analyzed using commercially available software (Philips Xcelera 3.2.1.712, Amsterdam, Netherlands, or GE EchoPac 3.1.3, Chicago, Illinois); standard criteria were used for measurement of left and right heart chambers.[15] The left ventricular (LV) ejection fraction (EF) was calculated using Simpson's biplane method; 7 patients had a single plane LVEF due to limited biplane images. The proximal RV outflow diameter was measured in the parasternal long axis view (RVPLAX), and RV basal and mid diameters and length were measured from the RV focused apical 4 chamber view.[15] RV end-diastolic and end-systolic area were measured,[15] and the RV fractional area change (RVFAC) was calculated. RV end-diastolic and end-systolic volumes were measured using a single plane method of discs. Tricuspid regurgitation (TR) velocity was measured from multiple views (parasternal long and short axis, and the apical 4 chamber and RV focused views). The highest TR velocity was used in the final analysis. Right atrial (RA) and left atrial (LA) maximal area were measured from the apical 4-chamber view at end systole. RA pressure was estimated from the inferior vena cava diameter and collapsibility with respiration.[15]

Categorical variables are expressed as frequencies/percentages, and continuous variables as mean ± standard deviation. Where appropriate, continuous variables were log transformed to approximate normality or to stabilize the variance before analysis. Student's *t* Test was used to compute unadjusted p values comparing the continuous variables between PE and control groups, and general linear models used to obtain p values adjusted for the covariate age. The area under the receiver operating characteristic curve was used to determine the optimal echocardiographic parameters for discriminating between PE patients and controls.

Parameters were evaluated for association with adverse events. Significant univariate echocardiographic parameters were divided into quartiles and Cox proportional hazard models were created to identify parameters that were significantly associated with mortality ($p < 0.1$). Analysis was performed using SPSS version 23.0 (IBM Inc., Armonk, New York). A p value of <0.05 was considered statistically significant.

Results

A total of 233 consecutive PE patients, with TTE performed during index hospital admission were included in the final analysis; the mean time to TTE from admission was 3.4 days. Clinical and demographic characteristics of PE patients are presented in Table 1. PE was confirmed by CTPA in 51%, by ventilation-perfusion scintigraphy in 43%, and 6% had both.

Echocardiographic parameters in PE patients and controls are shown in Tables 2A and 2B; as controls were younger than PE patients, unadjusted as well as age adjusted analysis was performed. As expected, PE patients

Table 1
Clinical, demographic, and outcome characteristics of PE patients

Parameter (mean ± SD) or number (%)	N = 233
Age (years)	66 ± 17
Males	99 (42 %)
Documented DVT during admission	70 (30 %)
Length of hospital stay (days)	10 ± 8
Coronary heart disease	26 (11 %)
Congestive cardiac failure	25 (11 %)
Atrial flutter/fibrillation	25 (11 %)
Valvular heart disease	8 (3 %)
Peripheral vascular disease	15 (6 %)
Stroke	4 (2 %)
Hypertension	44 (19 %)
Hyperlipidemia	17 (7 %)
Diabetes mellitus	30 (13 %)
Current smoker	23 (10 %)
Ex-smoker	43 (19 %)
Malignancy	26 (11 %)
Hypercoagulability	7 (3 %)
Reduced mobility	17 (7 %)
Previous pulmonary hypertension	3 (1 %)
Chronic pulmonary disease	13 (18 %)
Neurodegenerative disease	16 (22 %)
Chronic renal disease	17 (7 %)
Mean follow-up time (years)	3.0 ± 2.1
Death	61 (26 %)
Inpatient death	8 (3 %)
Outpatient death	53 (23 %)

DVT = deep vein thrombosis.

Table 2A
Left-sided and general echocardiographic parameters in controls and PE patients

Parameter	Controls(n = 70) (mean ± SD) or number (%)	PE (n = 233) (mean ± SD) or number (%)	p Value	
			Unadjusted	**Age-adjusted**
LA size				
LA area (cm^2)	18 ± 3	19 ± 5	0.478	0.663
LV size and function				
LV end diastolic volume (ml)	82 ± 23	108 ± 44	<0.001	<0.001
LV end systolic volume (ml)	33 ± 12	50 ± 35	<0.001	<0.001
LV ejection fraction (%)	59 ± 6	56 ± 12	0.066	0.047
Pressure estimates				
Peak TR velocity (ms^{-1})	2.1 ± 0.5	2.7 ± 0.7	<0.001	<0.001
IVC diameter (mm)	13 ± 5	17 ± 6	<0.001	<0.001
Estimated right atrial pressure >3 mm Hg	7 (10%)	79 (40%)	<0.001	<0.001
Estimated PASP (mm Hg)	24 ± 8	35 ± 18	<0.001	<0.001

IVC = inferior vena cava; LA = left atrium; LV = left ventricle; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation.

Table 2B
Right-sided echocardiographic parameters in controls and PE patients

Parameter	Controls(n = 70) (mean ± SD)	PE (n = 233) (mean ± SD)	p Value	
			Unadjusted	Age-adjusted
RA size				
RA area (cm^2)	15 ± 3	18 ± 6	<0.001	0.004
RA/LA ratio	0.83 ± 0.15	0.98 ± 0.38	<0.001	<0.001
RV size				
RV diameter parasternal long axis (mm)	30 ± 4	34 ± 6	<0.001	<0.001
RV base (mm)	33 ± 5.0	37 ± 7	<0.001	<0.001
RV mid (mm)	26 ± 4	32 ± 8	<0.001	<0.001
RV length (mm)	69 ± 7	71 ± 10	0.069	0.008
RV end-diastolic area (cm^2)	15 ± 3	22 ± 7	<0.001	<0.001
RV end-systolic area (cm^2)	9 ± 3	15 ± 6	<0.001	<0.001
RV end-systolic volume (ml)	14 ± 7	32 ± 21	<0.001	<0.001
RV end-diastolic volume (ml)	32 ± 13	56 ± 29	<0.001	<0.001
RV/LV ratio	0.3 ± 0.1	0.6 ± 0.4	<0.001	<0.001
RV function				
RV ejection fraction (%)	57 ± 9	44 ± 15	<0.001	<0.001
RV fractional area change (%)	41 ± 9.0	32 ± 12	<0.001	<0.001

LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

had enlarged right heart chambers (diameter, area, and volumes) with reduced RV function (RVEF and RVFAC). A significant difference in the RV/LV ratio and RA/LA ratio was observed between groups (Table 2B). The estimated pulmonary artery systolic pressure (peak TR velocity) was higher in the PE group (Table 2A). Receiver operating characteristic curves for parameters of RV size (RVPLAX diameter, RV area and volumes), and RV function (RVFAC and RVEF) were derived (Figure 1).

PE patients were subdivided into those who died (n = 61) versus those alive at 3-year follow up (n = 172). Echocardiographic parameters between the 2 subgroups are shown in Table 3. RA area, RVPLAX diameter, RV basal and mid diameter, RV end-diastolic and end-systolic volumes, RVEF, and TR velocity were significant univariate predictors of death, whereas RVFAC demonstrated a trend toward significance.

Significant parameters that were predictors of mortality by the Cox proportional hazard model were RVPLAX, RA area, and TR velocity, with increased mortality evident for the highest quartile for each variable. Hence, the 3 variables were dichotomized into the highest quartile versus the rest, for multivariate analysis. The highest quartile for each variable was an independent predictor of mortality in our group (RVPLAX [>37 mm] hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.3 to 4.2, p = 0.005, RA area [>20 cm^2] HR 2.0, 95% CI 1.1 to 3.5, p = 0.016, TR velocity (>2.9 ms^{-1}) HR 2.0, 95% CI 1.1 to 3.4, p = 0.021). When PE patients were divided into those with RVPLAX >37 mm and those ≤37 mm, RVFAC (27% vs 34%; p = 0.012) and RVEF (41% vs 46%; p = 0.048) were significantly reduced by Mann-Whitney *U* test.

The present study numbers were too small to examine independent versus combined effects of all the 3 echocardiographic variables (i.e., RVPLAX diameter, RA area, and TR velocity). Therefore, we evaluated the 3 "risk markers" in patients who died; mortality increased as the number of independent "risk markers" increased. When patients with

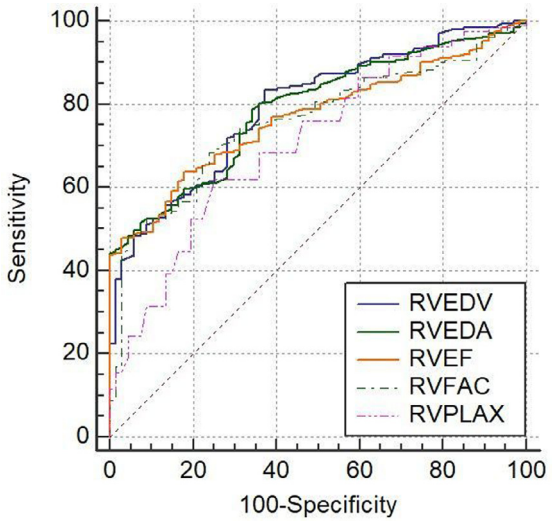


Figure 1. Receiver operating characteristics curves for RV size and functional parameters
RVEDV (AUC 0.793, SE 0.029) and RVEDA (AUC 0.788, SE 0.028) showed the highest AUC. Other AUCs were RVEF 0.77 (SE 0.03), RVFAC 0.76 (SE 0.03), and RVPLAX diameter 0.71 (SE 0.035). AUC = area under the curve, SE = standard error, RVEDV = right ventricle end diastolic volume, RVEDA = right ventricle end diastolic area, RVEF = right ventricle ejection fraction, RVFAC = right ventricle fractional area change, RVPLAX = right ventricle diameter in parasternal long axis view.

none of the 3 "risk markers" were compared with patients with 1 "risk marker," there was a 2-fold increase in mortality (HR 2.3, 95% CI 1.1 to 4.9; p = 0.033); patients with 2 "risk markers" had a 3-fold increase in mortality (HR 3.1, 95% CI 1.4 to 6.7; p = 0.005), whereas those with all 3 "risk markers" had a HR 16.9 (95% CI 6.1 to 47.2; p <0.001). Early mortality (1 year) was observed in patients with all 3 "risk markers," with 6 of 8 patients (75%), dying within the first year (Figure 2).

Table 3
Echocardiographic parameters in PE patients who died and those that survived

Parameter	No death (n = 172) (mean ± SD)	Death (n = 61) (mean ± SD)	p Value
Age (years)	63 ± 17	73 ± 13	<0.001
RA size			
RA area (cm^2)	17 ± 6	20 ± 6	0.003
RA/LA ratio	0.98 ± 0.39	1.01 ± 0.34	0.530
RV size and function			
RV diameter parasternal long axis (mm)	34 ± 6	36 ± 6	0.001
RV base (mm)	37 ± 7	39 ± 8	0.003
RV mid (mm)	32 ± 7	34 ± 8	0.033
RV length (mm)	71 ± 10	72 ± 11	0.905
RV end-diastolic area (cm^2)	21 ± 7	23 ± 7	0.073
RV end-systolic area (cm^2)	15 ± 6	17 ± 7	0.078
RV end-systolic volume (ml)	30 ± 19	39 ± 26	0.003
RV end-diastolic volume (ml)	53 ± 27	64 ± 32	0.018
RV/LV ratio	0.5 ± 0.3	0.6 ± 0.5	0.053
RV ejection fraction (%)	45 ± 15	42 ± 16	0.025
RV fractional area change (%)	32 ± 13	30 ± 11	0.051
Pressure estimates			
TR velocity (ms^{-1})	2.6 ± 0.7	2.9 ± 0.7	0.002
IVC diameter (mm)	16 ± 6	17 ± 4	0.143
Estimated PASP (mm Hg)	33 ± 17	39 ± 20	0.026
LA size			
LA area (cm^2)	18 ± 5	20 ± 7	0.003
LV size and function			
LV end-diastolic volume (ml)	106 ± 40	116 ± 56	0.190
LV end-systolic volume (ml)	47 ± 27	58 ± 50	0.073
LV ejection fraction (%)	56 ± 10	55 ± 16	0.619

IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RV = right ventricle; PASP = pulmonary artery systolic pressure; RA = right atrium; TR = tricuspid regurgitation.

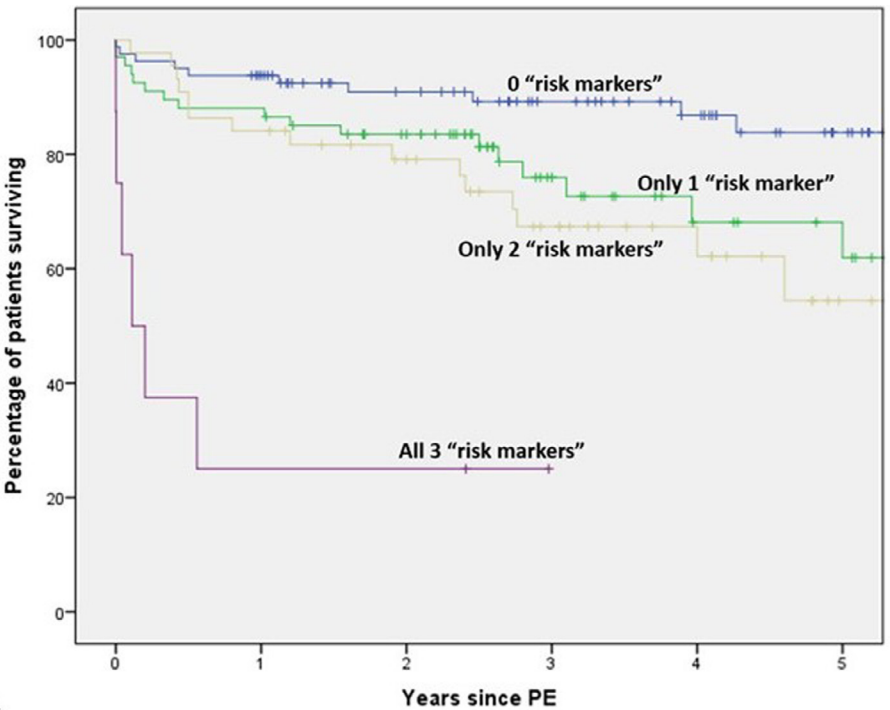
Discussion

We sought to identify echocardiographic determinants of long-term mortality in intermediate risk PE patients. In our PE cohort, 3 simple and routinely measured echocardiographic parameters, RVPLAX diameter >37 mm, RA area >20 cm^2 and TR velocity >2.9 ms^{-1}, were independent predictors of mortality; the composite of these parameters, when significantly altered, provided incremental prognostic value and may help identify high risk PE patients.

Guidelines recommend a TTE for risk stratification of intermediate risk PE patients.[4,5] However, as previously reported, TTE is not always performed[16]; moreover a specific time for performance of TTE following presentation with PE, has not been identified. Several studies have reported TTEs performed within 24 to 48 hours after presentation.[9,17] Our study reflects what likely occurs in "real world" practice, with TTE performed at a mean of 3.4 days. RV dysfunction is a determinant of early mortality; a meta-analysis of ~3,300 patients demonstrated a 2.6 times increase in early mortality with evidence of RV dysfunction on TTE.[7] Although studies have validated qualitative assessments of RV function in acute PE,[18] subjective evaluation relies on individual expertise.[19] Hence, we omitted qualitative measures, including McConnell's sign in the current analysis, to minimize observational bias.

Tricuspid annular plane systolic excursion (TAPSE) determines longitudinal RV function and predicts early mortality in PE.[6,20] However, TAPSE is angle dependent and measures RV basal segment function; TAPSE (performed in a subset of 134 patients), was not significantly reduced in PE patients who died. RV S' velocity derived from tissue doppler also evaluates basal RV systolic function. RV strain has also been a predictor of mortality in PE patients.[9,17] Although RV strain is a robust quantitative measure, it requires adequate 2D image quality, often a limitation particularly for evaluation of the RV free wall.

The pulmonary artery vasculature is a low pressure and low resistance system. An increase in pulmonary vascular resistance has been attributed to anatomical obstruction, release of vasoconstrictive agents, and reflex hypoxemia in PE. There is often a significant increase in RV afterload



No. at Risk						
0 "risk markers"	81	72	58	45	34	21
1 "risk marker"	67	59	48	24	14	10
2 "risk markers"	44	37	29	20	12	3
3 "risk markers"	8	2	2	0	0	0

Figure 2. Kaplan-Meir curves showing survival in patients with increasing number of "risk markers" (RVPLAX >37 mm, RA area >20 cm^2, and TR velocity >2.9 ms^{-1})

There was an increase in mortality risk as the number of independent "risk markers" increased. Patients with all three "risk markers" (RVPLAX >37 mm, RA area >20 cm^2, and TR velocity >2.9 ms^{-1}) had the highest risk of mortality. RA = right atrium, RVPLAX = right ventricle diameter in parasternal long axis view, TR = tricuspid regurgitation.

that is quantitatively measured from the peak TR velocity.[21] Increased TR velocity has been associated with mortality in PE.[9,20] Persistently elevated pulmonary pressures following PE result in RV and RA dilatation. Being thin-walled low-pressure chambers, they have limited capacity for increased pressures without structural remodeling. An increased RA/LA ratio was a predictor of mortality in PE patients.[22] However, following anticoagulation, acute recovery of RA/LA ratio within 24 hours, was observed.[22]

Acute mortality from PE is 5% to 11%,[1,3,8,14,23] with mortality in the first year approaching 25%.[18,23] However, the true disease burden is likely underestimated, with registries not accounting for patients in whom diagnosis of PE is made at autopsy[24]; a previous autopsy study demonstrated that only 32% of patients with major PE were assigned an accurate antemortem diagnosis.[25] Clinical composite scores (pulmonary embolus severity index (PESI) score or simplified PESI score), and several echocardiographic parameters (RV/LV ratio,[26] TAPSE[6] and RV strain,[17] have predicted early [30 day] mortality. However, studies evaluating longer term mortality are sparse, and have small patient numbers. 3D RVEF and RV free wall strain were determinants of 6 month mortality[9]; both techniques requiring specialised software for analysis. Another study of PE demonstrated that RV size (increased RV/LV ratio) and reduced TAPSE, were predictors of mortality at 15 months follow-up.[20] Our cohort from 2 tertiary centers represents one of the largest number of PE patients evaluated for long-term mortality. Patient inclusion mandated a definitive diagnosis of submassive PE, thereby reducing inclusion of patients with small or "probable" PE.

There is no consensus on which echocardiographic parameters best predict mortality in PE patients. In our cohort, although RVEF and RVFAC were impaired, they were not determinants of mortality. RV function is reduced early, with improvement thereof with appropriate therapy. This early RV dysfunction may not have been captured as TTEs were not performed early (24 to 48 hours), with a mean time to TTE of 3.4 days. However, right-sided chamber enlargement likely reflects persistent and more severe RV dysfunction, with a greater likelihood of elevated pulmonary pressures.

In a recent study of fibrinolysis therapy with intermediate risk PE patients, inclusion was based on specific criteria for RV dysfunction including one of the following: RVPLAX or parasternal short axis diameter >30 mm, RV to LV end-diastolic diameter >0.9, RV free wall hypokinesis and TR velocity >2.6 m/s.[27] RA size reflects both RV afterload and consequent RV dysfunction. As the RA is a

thin-walled structure, remodeling, and dilatation may be more evident. The RA/LA ratio demonstrated prognostic value only when the TTE was performed within 24 hours.[22] We hence included RA size, rather than the RA/LA ratio, as a marker of sustained pulmonary pressure elevation.

A composite of simple echocardiographic "risk markers" were predictors of long-term mortality, particularly when combined. These simple parameters can be easily obtained, and without utilizing specific offline software. Measuring the RV diameter in the parasternal window has previously demonstrated good intraclass correlation.[28] Our data also mirrors that of Fukuda et al who showed that the combination of RV metrics and an increased RA area predicted worse outcomes in patients with pulmonary hypertension.[29]

Our patients were treated in an era predating thrombolysis or mechanical aspiration; however, we were unable to collect specific data regarding patient therapy including anticoagulation. The retrospective nature of the study did not allow for standardized vital sign collection including blood pressure and oxygen saturation values precluding calculation of the PESI score. Several current echocardiographic parameters were unavailable; in particular, TAPSE and RV S' velocity were not routinely recorded. Strain analysis could not be performed due to limited frame rates in the stored images. Cardiac biomarkers were not routinely evaluated, although they have utility in PE.[23,30]

Our control group, were younger than the PE group; however, age adjusted analysis demonstrated similar results. Identification of controls who were clinically diagnosed with PE without evidence on V/Q scan or CTPA would have been an ideal control group; however, this could not be easily identified retrospectively. There were insufficient numbers to investigate cause-specific death rates, given that the total number of deaths was only 61. Finally, as the present study was limited to PE patients who underwent a TTE, there could be a potential selection bias. PE is a common cardiovascular problem and TTE is recommended for clinical evaluation. Three simple echocardiographic "risk markers"−−the RVPLAX diameter, RA area and peak TR velocity−−demonstrated incremental prognostic value for mortality, especially when combined. Application of these measures to identify PE patients at high risk may play a role in determining treatment strategies, monitoring, and follow up in PE patients.

Acknowledgment

The authors seek to acknowledge the contribution of Professor T Marwick with regards to preparation of this manuscript.

Disclosures

The authors have no conflicts of interest to disclose.

1. Belohlavek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Exp Clin Cardiol* 2013;18:129–138.
2. Mediratta A, Addetia K, Medvedofsky D, Gomberg−Maitland M, Mor−Avi V, Lang RM. Echocardiographic diagnosis of acute pulmonary embolism in patients with McConnell's sign. *Echocardiography* 2016;33:696–702.
3. Stergiopoulos K, Bahrainy S, Strachan P, Kort S. Right ventricular strain rate predicts clinical outcomes in patients with acute pulmonary embolism. *Acute Card Care* 2011;13:181–188.
4. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, Svitil P, Vonk Noordegraaf A, Zamorano JL, Zompatori M. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033–3069. 3069a-3069k.
5. Saric M, Armour AC, Arnaout MS, Chaudhry FA, Grimm RA, Kronzon I, Landeck BF, Maganti K, Michelena HI, Tolstrup K. Guidelines for the use of echocardiography in the evaluation of a cardiac source of embolism. *J Am Soc Echocardiogr* 2016;29:1–42.
6. Pruszczyk P, Goliszek S, Lichodziejewska B, Kostrubiec M, Ciurzynski M, Kurnicka K, Dzikowska-Diduch O, Palczewski P, Wyzgal A. Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism. *JACC Cardiovasc Imaging* 2014;7:553–560.
7. Cho JH, Kutti Sridharan G, Kim SH, Kaw R, Abburi T, Irfan A, Kocheril AG. Right ventricular dysfunction as an echocardiographic prognostic factor in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis. *BMC Cardiovasc Disord* 2014;14:64.
8. Dutta T, Frishman WH, Aronow WS. Echocardiography in the evaluation of pulmonary embolism. *Cardiol Rev* 2017;25:309–314.
9. Vitarelli A, Barillà F, Capotosto L, D'angeli I, Truscelli G, De Maio M, Ashurov R. Right ventricular function in acute pulmonary embolism: a combined assessment by three-dimensional and speckle-tracking echocardiography. *J Am Soc Echocardiogr* 2014;27:329–338.
10. Ng ACC, Chung T, Yong ASC, Wong HSP, Chow V, Celermajer DS, Kritharides L. Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. *Circulation Cardiovasc Qual Outcomes* 2011;4:122–128.
11. Jimenez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, Otero R, Monreal M, Muriel A, Yusen RD. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010;170:1383–1389.
12. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet* 2016;388:3060–3073.
13. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy P-M, Fine MJ. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Critic Care Med* 2005;172:1041–1046.
14. Hee L, Ng AC, Huang J, Chow V, Mussap C, Kritharides L, Thomas L. The contribution of cardiovascular mortality to long term outcomes in a relatively young demographic following acute pulmonary embolism: a validation study. *Int J Cardiol* 2015;199:13–17.
15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–271.
16. Bing R, Chow V, Lau JK, Thomas L, Kritharides L, Ng ACC. Prevalence of echocardiography use in patients hospitalized with confirmed acute pulmonary embolism: a Real-World Observational Multicenter Study. *PloS One* 2016;11:e0168554.
17. Dahhan T, Siddiqui I, Tapson VF, Velazquez EJ, Sun S, Davenport CA, Samad Z, Rajagopal S. Clinical and echocardiographic predictors of mortality in acute pulmonary embolism. *Cardiovasc Ultrasound* 2016;14:44.
18. McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. *Am J Cardiol* 1996;78:469–473.
19. Taylor RA, Moore CL. Accuracy of emergency physician-performed limited echocardiography for right ventricular strain. *Am J Emerg Med* 2014;32:371–374.
20. Khemasuwan D, Yingchoncharoen T, Tunsupon P, Kusunose K, Moghekar A, Klein A, Tonelli AR. Right ventricular echocardiographic

parameters are associated with mortality after acute pulmonary embolism. *J Am Soc Echocardiogr* 2015;28:355–362.
21. Shafiq Q, Moukarbel GV, Gupta R, Hernandez DA, Khouri SJ. Practical echocardiographic approach for risk stratification of patients with acute pulmonary embolism. *J Echocardiogr* 2016;14:146–155.
22. Chow V, Ng ACC, Chung T, Thomas L, Kritharides L. Right atrial to left atrial area ratio on early echocardiography predicts long-term survival after acute pulmonary embolism. *Cardiovasc Ultrasound* 2013; 11:17.
23. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension. *Circulation* 2011;123:1788–1830.
24. Dresden S, Mitchell P, Rahimi L, Leo M, Rubin-Smith J, Bibi S, White L, Langlois B, Sullivan A, Carmody K. Right ventricular dilatation on bedside echocardiography performed by emergency physicians aids in the diagnosis of pulmonary embolism. *Ann Emerg Med* 2014;63:16–24.
25. Nordstrom M, Lindblad B. Autopsy-verified venous thromboembolism within a defined urban population−the city of Malmo, Sweden. *APMIS* 1998;106:378–384.
26. Sanchez O, Trinquart L, Planquette B, Couturaud F, Verschuren F, Caille V, Meneveau N, Pacouret G, Roy PM, Righini M, Perrier A, Bertoletti L, Parent F, Lorut C, Meyer G. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. *Eur Respir J* 2013;42:681–688.
27. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, Bluhmki E, Bouvaist H, Brenner B, Couturaud F, Dellas C, Empen K, Franca A, Galie N, Geibel A, Goldhaber SZ, Jimenez D, Kozak M, Kupatt C, Kucher N, Lang IM, Lankeit M, Meneveau N, Pacouret G, Palazzini M, Petris A, Pruszczyk P, Rugolotto M, Salvi A, Schellong S, Sebbane M, Sobkowicz B, Stefanovic BS, Thiele H, Torbicki A, Verschuren F, Konstantinides SV, Investigators P. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402–1411.
28. Kopecna D, Briongos S, Castillo H, Moreno C, Recio M, Navas P, Lobo JL, Alonso-Gomez A, Obieta-Fresnedo I, Fernández-Golfin C. Interobserver reliability of echocardiography for prognostication of normotensive patients with pulmonary embolism. *Cardiovasc Ultrasound* 2014;12:29.
29. Fukuda Y, Tanaka H, Motoji Y, Ryo K, Sawa T, Imanishi J, Miyoshi T, Mochizuki Y, Tatsumi K, Matsumoto K, Shinke T, Emoto N, Hirata K. Utility of combining assessment of right ventricular function and right atrial remodeling as a prognostic factor for patients with pulmonary hypertension. *Int J Cardiovasc Imaging* 2014;30:1269–1277.
30. Ng ACC, Yong ASC, Chow V, Chung T, Freedman SB, Kritharides L. Cardiac troponin-T and the prediction of acute and long-term mortality after acute pulmonary embolism. *Int J Cardiol* 2013;165:126–133.