Re-Appraisal of Echocardiographic Assessment in Patients with Pulmonary Embolism: Prospective Blinded Long-Term Follow-Up

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ABSTRACT **Background:** Acute pulmonary embolism (PE) is considered to be one of the most common cardiovascular diseases with considerable mortality. Conflicting data imply possible role for echocardiography in assessing this disease.

Objectives: To determine which of the echo parameters best predicts short-term and long-term mortality in patients with PE.

Methods: We prospectively enrolled 235 patients who underwent computed tomography of pulmonary arteries (CTPA) and transthoracic Echocardiography (TTE) within less than 24 hours. TTE included a prospectively designed detailed evaluation of the right heart including right ventricular (RV) myocardial performance index (RIMP), RV end diastolic and end systolic area, RV fractional area change, acceleration time (AT) of pulmonary flow and visual estimation. Interpretation and performance of TTE were blinded to the CTPA results.

Results: Although multiple TTE parameters were associated with PE, all had low discriminative capacity (AUC < 0.7). Parameters associated with 30-day mortality in univariate analysis were acceleration time (AT) < 81 msec (P = 0.04), stroke volume < 44 cc (P = 0.005), and RIMP > 0.42 (P = 0.05). The only RV independent echo parameter associated with poor long-term prognosis (adjusted for significant clinical, and routine echo associates of mortality) was RIMP (hazard ratio 3.0, P = 0.04). The only independent RV echo parameters associated with mortality in PE patients were RIMP (P = 0.05) and AT (P = 0.05). The addition of RIMP to nested models eliminated the significance of all other parameters assessing RV function.

Conclusions: Doppler-based parameters like pulmonary flow AT, RIMP, and stroke volume, have additive value on top of visual RV estimation to assess prognosis in patients with PE.

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KEY WORDS: computed tomography pulmonary arteries (CTPA), doppler, echocardiography, pulmonary embolism, right ventricle

Acute pulmonary embolism (PE) is considered to be the third most common cardiovascular disease, following myocardial infarction and cerebral stroke [1,2]. If acute PE is not diagnosed in a timely manner, mortality rates range from 1–30% depending on right ventricle (RV) function [3-6]. Primary diagnosis of PE is based on history aided by scoring systems [7-9] and computed tomography (CT) with the injection of radiocontrast into the pulmonary arteries (CTPA). The risk stratification of PE is based on a combination of clinical parameters, biomarkers, and qualitative assessment of the right ventricle by transthoracic echocardiogram (TTE) [10-15]. Multiple parameters were assessed for prognostication of patients with PE, mostly based on assessment of RV size or radial contraction, with conflicting results [6,16]. Specific guidelines were published by the American Society of Echocardiography [17,18] and the European Society of Cardiology [19] for evaluating the function of the right side of the heart.

In the current work we prospectively studied patients presenting to the Tel Aviv Sourasky Medical Center with shortness of breath of unknown etiology. These patients underwent CTPA and TTE that included a prospectively designed RV focused echocardiogram protocol within 24 hours of arrival, as part of their clinical evaluation. Inerpretation of TTE was performed blinded to the CT results. Our goal was to determine which of the TTE parameters of the right side of the heart best predicts short and long-term mortality.

PATIENTS AND METHODS

STUDY DESIGN

Between January 2009 and December 2012 we initiated a prospective single center observational registry including patients presenting to our tertiary care emergency department (ED). The two first authors of the study (HS and AS) were notified by the ED consultants of all patients presenting with dyspnea of unknown origin in randomly selected weekdays. Referral for CTPA and echocardiogram studies was based on clinical suspicion of acute PE in patients with no contraindications (e.g.,

severe allergic reactions to iodine-containing contrast media or renal failure) based on the clinical judgment of the treating ED consultants. Once clinical need for CTPA and echocardiogram was affirmed, the study physicians were responsible of arranging the CTPA and echocardiogram within 24 hours of arrival to the center and that the echocardiogram was performed by one of the study sonographers (RM, YH, or EE) using a detailed evaluation of the right heart, blinded to the results of CTPA. They were also in charge that all echocardiogram studies were reviewed by a study senior cardiologist (SB or YT) blinded to the CTPA results and the patient's history.

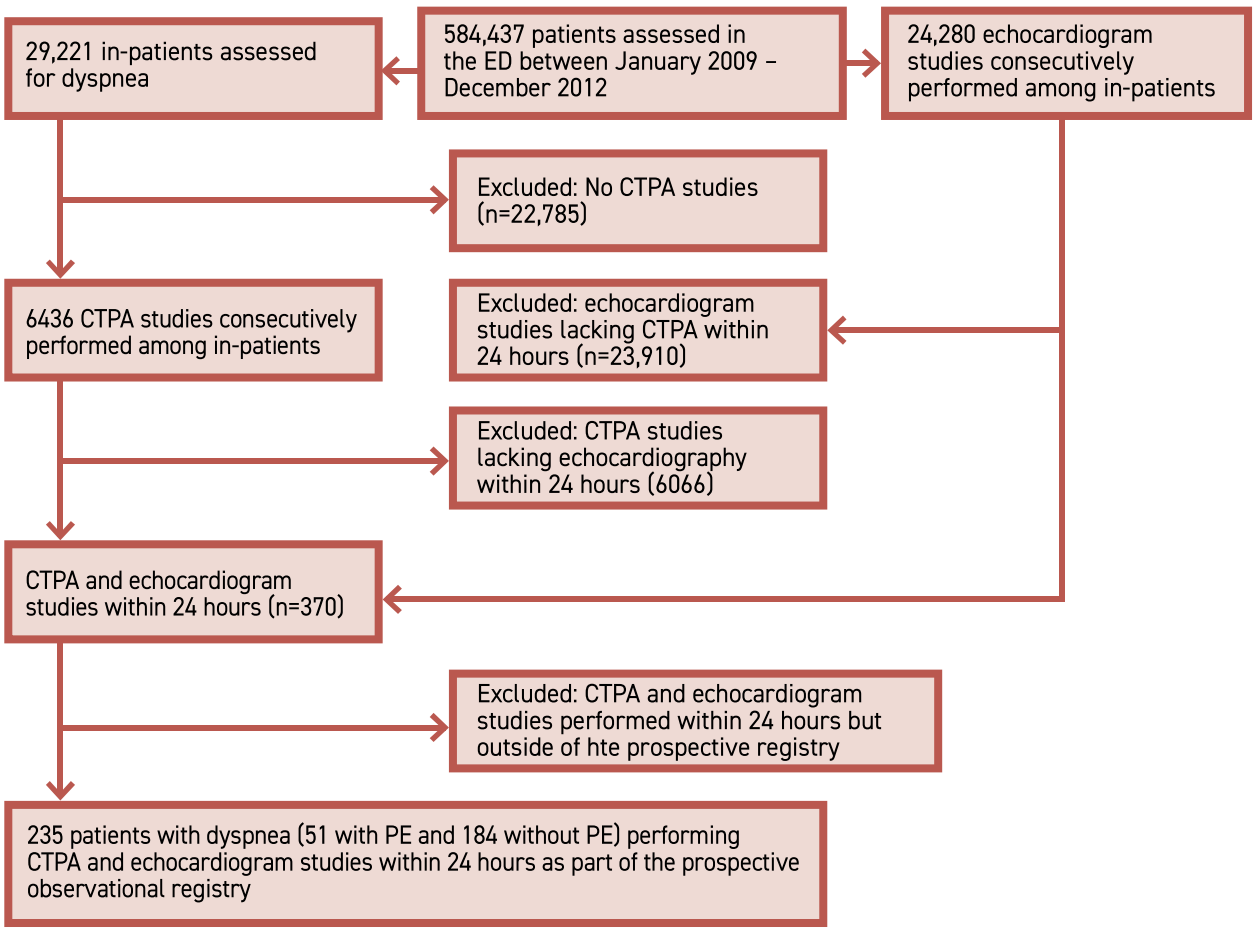
The records of all patients were reviewed retrospectively. Co-morbid conditions, medications, related physical examination findings, and demographic data were retrieved from the records without patient contact. Outcome was analyzed from the day of admission until death or last follow-up. Follow-up ended by April 2017. The ethics committee at the Tel Aviv Sourasky Medical Center approved the study protocol.

The patient selection flow chart is shown in Figure 1.

COMPUTED TOMOGRAPHY PULMONARY ARTERIES

All patients were imaged with a multi-detector CT scanner (Brilliance or Mx8000 IDT; Philips Medical Systems, Cleveland, Ohio, USA) with 64 or 16 detector rows by using a CT pulmonary angiographic electrocardiographically gated protocol, with contrast material injections of 70–100 ml (Ultravist; Schering, Berlin, Germany). Automated bolus tracking was used with a region of interest placed in the main PA. CT scanning was performed in a caudal-cranial direction during breath hold, with coverage of the chest from the base of the lungs to the thoracic inlet. The CT studies were all reviewed by a senior radiologist blinded to the echocardiograph results.

Figure 1. Flowchart showing patient selection



CTPA = computed tomography pulmonary arteries, ED = emergency department, PE = pulmonary embolism

TRANSTHORACIC ECHOCARDIOGRAPHY

All patients underwent a transthoracic echocardiogram (TTE) and Doppler TTE study with multiple windows during the same examination including a detailed evaluation of the right heart. All the echocardiogram examinations were performed with the same equipment (iE33, Philips Medical Systems) and with the S3 probe for two-dimensional images.Apart from qualitative grading of RV size and function, the RV size was evaluated by RV end diastolic area, RV end systolic area, right to left end diastolic diameter ratio (4 chamber view) and RV end diastolic diameter (in the para-sternal long axis view). Moreover, RV function was assessed by the RV myocardial performance index (RIMP), RV fractional area change (RVFAC), pulmonic flow acceleration time (AT), the 60/60 sign, the D sign and the McConnell's sign. RIMP is a global estimate of both systolic and diastolic function of the right ventricle and was defined as the (Isovolumic relaxation time + Isovolumic contraction time) / Ejection time. RVFAC was obtained by tracing the endocardium in the 4 chamber view from the annulus along the the free wall to the septum and then back to the annulus both in systole and diastole and using the formula RVFAC = [(RV end diastolic area- RV end systolic area)/RV end diastolic area] × 100. The 60/60 sign was defined as the coexistence of shortened pulmonary ejection time (AT < 60 msec) and systolic pulmonary pressure < 60 mmHg. McConnell's sign was defined as hypokinesis of the RV free wall with normal contraction of the apical segment. The D sign was defined in the short axis whenever the left ventrcile assumed a more D shaped cavity in the short axis loosing its convexity with respect to the center of the RV cavity during diastole [18,20]

STATISTICAL ANALYSIS

Comparison between the two groups (those with and those without PE) was obtained using the Wilcoxon and *t*-tests. Categorical data compared beween the groups using the Chi-square test or the Fisher exact test, where the expected value in each cell is less than 5. To assess independent relation with PE, a univariable analysis based on logistic regression models was conducted (with diagnosis of PE as dependent variable and echocardiographic parameters as independent sequental variables). A receiver operating characteriostics (ROC) analysis was used to determine the optimal values of the sequental variables to predict diagnosis of PE (the value with highest sensitivity and specificity). The AUC (area under the curve) was used to quantify the variables' ability to predict diagnosis of PE. To analyze independent determinants of all cause mortality multivariate Cox Hazard analysis was performed. Clinical parameters (age, HTN, COPD, CHF, malignancy) and variables assessing general echocardiogram predictors (E/A ratio, SPAP, RA pressure, stroke volume) were entered first. The first entry criterion in the multivariate analysis was a univariate $P < 0.05$. To correct for possible overfitting of the model and to avoid multicollinearity, we used correlation factor analyses to determine if any pairs of predictor variables were highly correlated (correlation coefficients over 0.9) and therefore likely to result in multicollinearity. If any such pairs were found, one of the predictor variables was selected for inclusion in the final analysis and the other was ignored. The variable with the lowest *P* value was chosen to be included in the analysis. We then entered the parameters measuring right-heart size, or function consecutively to the model. All data were analyzed with the JMP 12 by SAS Institute Inc., Cary, NC, USA. $P < 0.05$ was considered to indicate statistical significance. All authors participated in collecting the data, designing the study, and revising the manuscript draft.

RESULTS

Baseline clinical and TTE parameters satratified by presence or absence of PE are presented in Table 1. The cohort included 235 subjects (mean age 66.8 ± 18, 37% males) of which 51 (22%) had PE. In the entire cohort 4 patients presented with shock (1 in the PE group and 3 in the non-PE group), and another 8 patients were admitted to the intensive care unit (3 in the PE group and 5 in the non-PE group). The reasons for admission to intensive care were sepsis (n=4), hemmorage requiring multiple blood transfusions (n=2), and RV dysfunction in qualitative TTE analysis (n=2). The final diagnosis in the non-PE patients were acute respiratory infections (n=55), obstructive lung disease exacerbation (n=20), acute coronary syndrome (n=27), bleeding event (n=9), acidosis (n=8), arrhythmic event (n=4), acute neurologic event (n=5), lung cancer (n=5), rheumatic disease (n=4), and dyspnea without apparent cause (n=44). In the PE group 43 had low risk PE, 4 had intermediate low risk PE, 3 had intermediate high risk PE, and only one had high risk PE requiring thrombolysis. Patients with diagnosis of PE on CTPA had a lower E wave velocity, lower E/A mitral inflow ratio, smaller LA volume, shorter acceleration time, higher incidence of D sign, 60/60 sign and McConnell's sign on echocardiography, as well as lower prevalence of heart failure, renal failure, and diabetes. Although multiple TTE parameters were associated with PE, all had low discriminative capacity [Table 1].

TTE PARAMETERS ASSESSING SHORT TERM MORTALITY RISK

Fifteen patients (6.5%) from the entire cohort died in the 30-day period after admission. The TTE parameters associated with increased risk of immediate death in the entire cohort were AT < 81 msec (sensitivity 63%, specificity 73%, $P = 0.04$), McConnell's sign (sensitivity 36%, specificity 87%, $P = 0.04$), stroke volume < 44 cc (sensitivity 87%, specificity 59%, $P = 0.0004$), systolic pulmonary pressure > 48 mmHg (sensitivity 77%, specificity 84%, $P < 0.0001$), TR peak velocity > 2.6 m/sec (sensitivity 100%, specificity 49%, $P = 0.0004$), right-to-left ventricular end-diastolic diameter ratio > 0.9 (sensitivity 43%, specificity 87%, $P = 0.007$), RIMP > 0.42 (sensitivity 67%, specificity 74%, $P = 0.005$), qualitatively estimated moderate or severe RV dilatation (sensitivity 50%, specificity 82%, $P = 0.01$), but not

Table 1. Baseline clinical and echocardiogram parameters stratified by presence or absence of pulmonary embolism

Variable	All (n=232)	PE (n=51)	Non-PE n=181)	*P* value
Age, years	67 ± 18	65 ± 17	67 ± 17	0.5
Gender, male	37%	41%	35%	0.5
Heart rate	80.1 ± 8	81.7 ± 11	79.7 ± 7	0.2
Weight	71.7 ± 17	73.3 ± 16	71.3 ± 17	0.5
Height	163.8 ± 15	164.8 ± 8	163.6 ± 16	0.6
Body surface area	1.77 ± 0.2	1.79 ± 0.2	1.76 ± 0.2	0.4
Obesity	14%	13%	14%	0.9
Diabetes mellitus	23%	13%	26%	0.05
Hypertension	52%	45%	54%	0.2
Smoker	22%	8%	25%	0.03
IHD	22%	14%	24%	0.1
Cerebrovascular accident	11%	8%	12%	0.4
Recent infection	16%	18%	15%	0.5
Recent surgery	13%	20%	11%	0.1
Mechanical ventilation	6%	8%	5%	0.5
Intensive care admission	6%	8%	5%	0.4
Dyslipidemia	40%	35%	42%	0.3
COPD	29%	15%	33%	0.01
Congestive heart failure	13%	7%	14%	0.2
Chronic renal failure	8%	2%	10%	0.02
Malignancy	25%	31%	23%	0.2
Hemoglobin	12 ± 1.8	12 ± 1.6	12 ± 1.9	0.8
Creatinine, mg/dl	1.1 ± 0.6	1.06 ± 0.2	1.1 ± 0.7	0.4
CRP, mg/L	65 ± 67	88 ± 71	59 ± 65	0.03
Troponin level, ng/L	81 ± 463	103 ± 530	75 ± 443	0.7
EF %	57.8 ± 6	58.7 ± 3	57.6 ± 7	0.2
LA Volume	71.9 ± 41	60.5 ± 32	75.2 ± 43	0.01
RA area	17 ± 6	17 ± 7	17 ± 6	0.8
LVEDD cm	4.7 ± 0.7	4.7 ± 0.7	4.7 ± 0.7	0.8
LVESD cm	2.8 ± 0.7	2.7 ± 0.7	2.8 ± 0.7	0.5
LV mass gr	177 ± 74	175 ± 70	177 ± 75	0.9
Stroke volume cc	47.4 ± 18	45.7 ± 14	47.9 ± 18	0.4
Stroke volume index	26.1 ± 9	25.0 ± 6	26.3 ± 9	0.3
E'	5.9 ± 2.1	5.5 ± 2.8	6.1 ± 1.8	0.6
E wave	0.84 ± 0.31	0.74 ± 0.22	0.86 ± 0.32	0.006
A wave	0.82 ± 0.24	0.85 ± 0.21	0.81 ± 0.25	0.5
E/A ratio	1.1 ± 0.7	0.9 ± 0.4	1.16 ± 0.7	0.008
SPAP mmHg	37 ± 18	40 ± 20	37 ± 17	0.4
RIMP	0.37 ± 0.2	0.4 ± 0.3	0.4 ± 0.3	0.7
RV end diastolic area cm2	15.5 ± 5	15.5 ± 5	15.5 ± 5	0.9
RV end systolic area cm2	9.3 ± 4	9.2 ± 4	9.2 ± 5	0.9
RV fractional area change	42 ± 11	42 ± 11	42 ± 12	0.7
Declaration time, msec	200 ± 64	190 ± 65	204 ± 63	0.2
PA diameter	2.6 ± 2	2.5 ± 0.4	2.6 ± 2	0.7
AT ms	96.5 ± 28	85 ± 29	100 ± 27	0.01
AT/RR interval	129 ± 48	119 ± 49	131 ± 47	0.1
RV end diastolic diameter cm	3.2 ± 0.8	3.2 ± 0.7	3.2 ± 0.8	0.4
LV end diastolic diameter cm	4.1 ± 0.7	4 ± 0.7	4.1 ± 0.7	0.4
RVEDD/LVEDD > 0.9	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.8
LVED/RVED > 0.9	14%	16%	14%	0.7
Sign 60/60	14%	31%	9%	0.0002
IVC expiratory diameter cm	1.8 ± 1.4	1.6 ± 0.5	1.8 ± 1.6	0.2
IVC inspiratory diameter cm	1 ± 1.7	0.9 ± 0.5	1.1 ± 1.9	0.3
RA pressure mmHg	8 ± 4.5	8 ± 4.5	8.5 ± 4.5	0.4
McConnell's sign	14.68%	40%	7.65%	0.001
D sign	11.87%	20.41%	9.41%	0.05

AT = acceleration time, COPD = Chronic obstructive pulmonary disease, CHF = congestive heart failure, CRF = chronuc renal failure, CRP = C-reactive protein, EF = ejection fraction, IHD = ischemic heart disease, IVC = inferior vena cava, SPAP = systolic pulmonary pressure, LA = left atrium, LV = left ventricle, PA = pulmonic artery, PE = pulmonary embolism, RA = right atrium, RIMP = right ventricle myocardial performance index, WBC = white blood cells

Table 2. Parameters associated with long-term mortality in patients with pulmonary embolism

Variable	Hazard ratio for mortality	Lower 95%	Upper 95%	*P* value
Age, years	1.06	1.03	1.09	< 0.0001
Gender, male	0.92	0.41	2.07	0.8
Heart rate	1.00	0.97	1.05	0.8
Weight	0.95	0.91	0.99	0.02
Height	0.97	0.92	1.03	0.3
Body surface area	0.1	0.002	0.7	0.02
Diabetes mellitus	1.23	0.36	3.26	0.7
Hypertension	1.71	0.77	3.87	0.2
Smoker	2.5	0.94	6.3	0.07
IHD	3.1	1.1	7.9	0.03
Past cerebrovascular accident	1.3	0.2	4.5	0.7
Recent infection	1.15	0.3	3.2	0.8
Recent surgery	1.03	0.3	2.9	0.9
Mechanical ventilation	1.08	0.32	6.8	0.9
Sepsis or hemorrhage	0.06	0.001	0.81	0.03
COPD	3.56	1.33	8.79	0.01
Congestive heart failure	6.38	1.79	18.03	0.007
Chronic renal failure	1.44	0.49	2.7	0.3
Malignancy	2.24	0.99	4.96	0.05
Hb	0.9	0.7	1.16	0.4
Creatinine mg/dl	3.98	0.72	18.72	0.1
CRP mg/L	0.99	0.99	1	0.5
EF %	0.89	0.8	1.03	0.1
LA volume	1.01	1.00	1.01	0.5
RA area	1.03	0.96	1.1	0.3
LVESD cm	1.8	0.86	3.22	0.1
LV mass gram	1	0.99	1.02	0.2
Stroke volume	0.96	0.93	0.98	0.006

Variable	Hazard ratio for mortality	Lower 95%	Upper 95%	*P* value
E'	0.85	0.53	1.12	0.3
E wave	0.98	0.96	1	0.2
A wave	1	0.99	1.04	0.1
E/A ratio	0.38	0.09	1.25	0.1
SPAP mmHg	1.00	0.98	1.03	0.3
RIMP	10.71	2.09	53.1	0.006
RV end diastolic area cm^2	1.04	0.94	1.14	0.3
RV end systolic area cm^2	1.08	0.97	1.18	0.1
RV fractional area change	0.96	0.93	1	0.08
RV size	2.01	0.87	4.44	0.09
RV function	1.8	0.52	4.76	0.3
Decelaration time msec	0.99	0.98	1	0.09
PA diameter	2.05	0.55	7.31	0.3
AT ms	0.76	0.59	0.94	0.01
AT/ RR interval	0.85	0.76	0.99	0.05
RV end diastolic diameter cm	0.93	0.5	1.65	0.8
LV end diastolic diameter cm	1.03	0.5	2.06	0.9
RVEDD/LVEDD	2.35	0.41	10.31	0.3
RVEDD/LVEDD > 0.9	2.77	1.06	6.46	0.03
RA/LA ratio	0.67	0.08	2.88	0.6
60/60 sign	8.6	1.7	33	0.01
IVC expiratory diameter, cm	1.66	0.58	4.66	0.3
IVC inspiratory diameter, cm	2.69	0.87	7.05	0.08
RA pressure	1.04	0.92	1.16	0.4
McConnell's sign	1.41	0.62	3.16	0.4
D sign	2.61	1.06	5.93	0.03
E wave × AT	0.99	0.98	0.99	0.002
E wave × stroke volume	0.95	0.92	0.99	0.006

AT = acceleration time, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, EF = ejection fraction, IHD = ischemic heart disease, IVC = inferior vena cava, SPAP = systolic pulmonary pressure, LA = left atrium, LV = left ventricle, PA = pulmonic artery, RA = right atrium, RIMP = right ventricle myocardial performance index

Table 3. Univariate analysis for cardiac mortality in pulmonary embolism patients

Variable	Hazard ratio	Lower 95%	Upper 95%	*P* value
Age, years	1.1	1.03	1.2	0.0007
Gender, male	0.45	0.1	1.9	NS
%EF	0.96	0.74	1.6	NS
LA volume	1.01	0.99	1.03	NS
RA area	1.17	1.06	1.32	0.004
LVEDD	0.96	0.3	3.2	NS
LVESD	2.7	1.1	6.1	0.03
LV mass, gram	1.02	1.00	1.06	0.02
Stroke volume	0.49	0.3	0.8	0.004
E/A ratio	0.32	0.1	2.2	NS
SPAP	1.44	1.00	2.06	0.05
RIMP	61	19	111	< 0.0001
RVEDA cm^2	1.2	1.06	1.38	0.005
RVESA cm^2	1.28	1.11	1.48	0.001
RVFAC %	0.92	0.88	0.97	0.005
RV size qualitative	4.8	1.19	23	0.03
RV function qualitative	5.1	1.18	35	0.03
AT ms	0.52	0.29	0.8	0.001
RV end diastolic diameter cm	2.87	1.12	7.6	0.03
RVEDD/LVEDD	16	1.5	156	0.03
RA/LA ratio	1.8	0.15	9.5	NS
60/60 sign	5.6	1.1	41	0.04
IVC inspiratory diameter cm	4.2	0.98	15	NS
RA pressure ≥ mmHg10	1.07	0.88	1.25	NS
McConnell's sign	1.7	0.4	7.1	NS
D sign	5.3	1.2	23	0.03
E wave × AT	0.99	0.98	0.99	0.007
E wave × stroke volume	0.98	0.98	0.99	0.001

LA = left atrium, RA = right atrium, LVEDD = left ventricle end diastolic diameter, LVESD = left ventricle end systolic diameter, SPAP = systolic pulmonary artery pressure, RIM*P* = right index myocardial performance, RVEDD = right ventricle end diastolic diameter, RVESD = right ventricle end systolic diameter, RVFAC = right ventricle fractional area change, AT = acceleration time, IVC = inferior vena cava

qualitative assessment of RV dysfunction, RV end diastolic area, RV end diastolic diameter > 30 mm, end systolic area, or RV fractional area change.

Five patients (10%) from the PE patients died in the 30-day period after admission. The only univariate TTE parameters associated with increased risk of immediate death in the PE patients were AT < 81 msec (sensitivity 100%, specificity 51%, $P = 0.04$), stroke volume < 44 cc (sensitivity 100%, specificity 57%, $P = 0.005$), and RIMP > 0.42 (sensitivity 75%, specificity 74%, $P = 0.05$), but not systolic pulmonary pressure, TR peak velocity, qualitatively estimated RV dilatation or dysfunction, RV end diastolic area, RV end diastolic diameter, end systolic area, right-to-left ventricular end-diastolic diameter ratio > 0.9, or RV fractional area change.

TTE PARAMETERS ASSOCIATED WITH LONG-TERM SURVIVAL

During the follow-up period (4.4 ± 2.7 years) 117 deaths occurred. Clinical and TTE parameters associated with long-term mortality in patients with PE are shown in Table 2. The TTE parameters associated with mortality in the PE patients were high RIMP

(P = 0.006), low stroke volume (P = 0.007), short acceleration time (P = 0.01), D sign (P = 0.04), right-to-left ventricular end-diastolic diameter ratio> 0.9 (P = 0.03), but not systolic pulmonary pressure, qualitatively estimated RV dilatation or dysfunction, RV end diastolic area, end systolic area or RV fractional area change.

The addition of RIMP in nested models to other parameters of RV size or function including qualitative estimation, right to left ventricular end diastolic diameter ratio, or RV fractional area change eliminated the significance of all other parameters and improved the prediction of the models (P < 0.05 for all comparisons). Because only 29 patients in the PE group died during follow-up, we have limited the multivariable analysis for long-term mortality in PE patients to one parameter assessing RV function at a time, one assessing general echocardiogram assessment, and age. In multivariable analysis the only RV-related independent parameters associated with all cause mortality in the PE group were RIMP (hazard ratio [HR] 5.6, 95% confidence interval [95%CI] 1.00–42, P = 0.05), and AT (HR 0.73, 95%CI 0.51–.99, P = 0.05). All other RV related parameters including RVFAC, McConnell's sign, D sign, and LVEDD/RVEDD ratio became insignificant when adjusted for clinical and general echocardiogram parameters.

Nine patients in the PE group died due to cardiovascular causes during follow-up (six due to progressive right ventricular failure and three due to witnessed cardiac arrest). The remaining patients died due to cancer (n=10), infection (n=5), and unknown cause (n=5). The results of Cox hazard analysis for cardiac mortality in PE patients are presented in Table 3. The RV-related TTE parameters associated with mortality in the PE patients were high RIMP (P < 0.0001), low stroke volume (P = 0.004), short acceleration time (P = 0.0001), D sign (P = 0.03), RV end diastolic area (P = 0.005), end systolic area (P = 0.001), RVFAC(P = 0.005), and RV end diastolic to LV end diastolic ratio (P = 0.03).

DISCUSSION

The main conclusion of this study is that several Doppler echocardiographic measures (RIMP, AT, and stroke volume) are significant correlates of prognosis in patients with PE and have additive value in assessment of patients with PE in addition to routine RV echocardiogram parameters (visual estimation of RV size, RV function, or measures of radial contraction).

Previous studies assessed the ability of different TTE measurements to evaluate patients with pulmonary embolism [21,22]. In most of these trials, the analyses were not prospective and were not blinded, thus echocardiogram analysis was performed retrospectively after the patients were identified to have (or not to have) PE. Our research has several advantages. First, it is prospective, thus RV assessment was comprehensive and included RV focused images and Doppler measurements, as suggested by recent guidelines [18]. Second, echocardiogram analysis was performed blindely without knowing if the patient had, or did not have PE, thus assessment of the different echocardiographic measures to reliably assess PE, and to evaluate their prognostic value was not biased. Third, the follow-up period was prolonged, enabling association analysis of the different echocardiogram parameters with long-term outcome and not just with immediate survival.

ECHOCARDIOGRAPHIC RISK STRATIFICATION

Previous studies assessing the role of echocarediography in the risk stratification of patients with PE had conflicting results with some showing that right-sided heart failure is associated with increased mortality [16,23] while others suggested that echocardiogram assessment did not add more valuable data than clinical evaluation [6]. These studies were mostly based on assessment of RV systolic pressure (using the TR velocity), quantitative visual assessments, or parameters based on measurement of RV size (RV end diastolic diameter, right-to-left ventricular end-diastolic diameter ratio).

In the current study we showed that in patients with PE, some of the best parameters associated with short-term and long-term prognosis were Doppler based variables (RIMP, AT, and stroke volume). The added value of these Doppler-based parameters in patients with PE may be explained by several factors. First, in patients with PE, especially when imaging is performed during tachypnea, visualization of the RV can be complex and problematic even if the exam is performed using RV focused views. However, Doppler parameters, especially those that are based on timing like RIMP, can be beneficial because they avoid the geometric assumptions and limitations of complex RV geometry [18]. Second, the Doppler parameters associated with increased mortality in patients with PE included low E wave velocity, short AT and low stroke volume. From a physiologic standpoint, these findings suggest low pressure in the left atrium (low E wave velocity) due to under-filling, increased pulmonary resistance (shorter acceleration time over the pulmonic valve), and poor RV function (high RIMP), resulting in low stroke volume, all characteristic of large hemodynamically significant PE.

Of note, although high pulmonary pressures are associated with excess mortality in patients with dyspnea from other causes [24,25], they were not asscoiated with outcome in patients with acute PE. We believe that this lack of association in this setting is because of the sudden increase in RV after-load, which may cause an acute insult to the RV, resulting with RV being unable to generate high pressure. This mechanism is in marked contrast to patients with other mechanisms for dyspnea (group 2 or group 3 of pulmonary hypertension), in whom higher TR velocity is a surrogate for higher left sided pressure (for group 2), or higher pulmonary vascular resistance (for group 3).

DIAGNOSIS OF PULMONARY EMBOLISM BY ECHOCARDIOGRAPHY

In the past, many TTE parameters were described as having reasonable sensitivity and specificity for diagnosis of pulmonary

embolism. These included McConnell's sign, D sign, or 60/60 sign [15,21]. Most of these studies were retrospective and not blinded. According to the current study, although specificity for some of these measures was reasonable, for all parameters AUC of the ROC graph were mediocre and sensitivity was low. We believe that these echocardiogram parameters are helpful, if present, for raising the possibility of PE and the need for further testing, but because of the low sensitivity echocardiogram cannot be used to diagnose or rule out PE.

LIMITATIONS

Because of the small number of events we were unable to perform multivariate analysis for 30-day mortality and some potentially important associations may have been neglected. By enrolling non-consecutive patients and having referring ED physicians decide to order TTE and CT, the cohort may have been enriched for PE by clinical suspicion.

CONCLUSIONS

Doppler based parameters like pulmonary flow AT, RIMP, and stroke volume, have significant additive value on top of visual RV estimation to assess prognosis in patients with PE.

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It is a capital mistake to theorize before one has data.Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.

Arthur Conan Doyle (1859–1930), British writer and medical doctor, created the character Sherlock Holmes

It is better to fail in originality than to succeed in imitation.

Herman Melville (1819–1891), American novelist, short story writer, essayist, and poet