A Doppler Echocardiographic Pulmonary Flow Marker of Massive or Submassive Acute Pulmonary Embolus

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Background: To date, echocardiography has not gained acceptance as an alternative imaging modality for the detection of massive pulmonary embolism (MPE) or submassive pulmonary embolism (SMPE). The objective of this study was to explore the clinical utility of early systolic notching (ESN) of the right ventricular outflow tract (RVOT) pulsed-wave Doppler envelope in the detection of MPE or SMPE.

Methods: Two hundred seventy-seven patients (mean age, 56 ± 16 years; 52% women), without known pulmonary hypertension, who underwent contrast computed tomographic angiography for suspected pulmonary embolism (PE) and underwent echocardiography were retrospectively studied. Extent of PE was categorized using standard criteria. ESN identified from pulsed-wave spectral Doppler interrogation of the RVOT was analyzed, as were other echocardiography parameters such as McConnell's sign, the "60/60" sign, and acceleration and deceleration times of the RVOT Doppler signal. Analysis was conducted using probability statistics and receiver operating characteristic curve analysis.

Results: Of the 277 patients studied, 100 (44%) had MPE or SMPE, 87 (38%) had subsegmental PE, and 90 (39%) did not have PE. ESN was observed in 92% of patients with MPE or SMPE, 2% with subsegmental PE, and in no patients without PE. Interobserver assessment of early systolic notching demonstrated 97% agreement ($\kappa = 0.93$, $P < .001$). Compared with more widely recognized echocardiographic parameters, the area under the receiver operating characteristic curve (AUC) of 0.96 (95% CI, 0.92–0.98) for ESN was superior to that for McConnell's sign (AUC, 0.75; 95% CI, 0.68–0.80), the 60/60 sign (AUC, 0.74; 95% CI, 0.68–0.79), and RVOT acceleration time ≤ 87 msec (AUC, 0.84; 95% CI, 0.79–0.88), as well as other study Doppler variables, in patients with computed tomography–confirmed MPE or SMPE.

Conclusions: The pulmonary Doppler flow pattern of ESN appears to be a promising noninvasive sign observed frequently in patients with MPE or SMPE. Future prospective study to ascertain diagnostic utility in a broader population is warranted. (J Am Soc Echocardiogr 2019;32:799-806.)

Keywords: Echocardiography, High-risk pulmonary embolism, Doppler notching, Pulmonary embolism

Pulmonary embolism (PE) is a common and potentially lethal medical condition that accounts for the hospitalization or death of >250,000 people in the United States annually.[1,2] The reported in-hospital mortality of patients with massive PE (MPE) varies from 25% to 50%, whereas mortality for submassive PE (SMPE; defined as the presence of right ventricular [RV] dysfunction without systemic

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Conflicts of Interest: None.

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Abbreviations

AT = Acceleration time

CTA = Computed tomographic angiography

ESN = Early systolic notching

MPE = Massive pulmonary embolism

PE = Pulmonary embolism

PVR = Pulmonary vascular resistance

PW = Pulsed-wave

ROC = Receiver operating characteristic

RV = Right ventricular

RVOT = Right ventricular outflow tract

SMPE = Submassive pulmonary embolism

SSPE = Subsegmental pulmonary embolism

hypotension) ranges from 3% to 15%, and that associated with low-risk or subsegmental PE (SSPE) is <5%.[3] Diagnostic and treatment algorithms for PE have been developed and endorsed by societies such as the European Society of Cardiology and the American Heart Association.[3,4]

Multidetector row computed tomographic angiography (CTA) and, to a lesser extent, ventilation-perfusion lung scanning are traditionally the most frequently used noninvasive imaging procedures for the diagnosis of acute PE. Given the high mortality associated with undiagnosed PE, it is imperative to risk-stratify acute PE expeditiously to ensure prompt initiation of anticoagulant therapy in appropriate cases and, conversely, refrain from initiating such therapy when not indicated.

The role of echocardiography in the workup of suspected PE has historically been supportive and primarily reserved for the detection of RV strain or dysfunction in unstable patients. In this context, a few echocardiographic parameters, such as McConnell's sign, the "60/60" sign, and RV dysfunction, have been studied, but their clinical utility has remained limited.[5,6]

We recently reported preliminary pilot data on the potential value of commonly used as well as less well recognized RV outflow tract (RVOT) Doppler variables, in patients with MPE or SMPE.[7] The present study expands on these observations and provides a head-to-head comparative assessment on the performance of several echocardiographic variables in a cohort of patients with MPE or SMPE identified following CTA for suspected PE.

METHODS

This retrospective investigation was approved by the Wayne State University institutional review board. All cases of contrast CTA performed for suspected PE at our tertiary care institution between 2015 and 2017 were reviewed. For inclusion in this study, all patients were required to have undergone transthoracic echocardiography within 48 hours of computed tomographic angiographic diagnosis of PE. Only patients with complete echocardiographic examinations, including interpretable pulsed-wave (PW) Doppler signals across the RVOT, measurable tricuspid regurgitation jet Doppler signals, and discernible endocardial border definition of the right ventricle, were included. Technically suboptimal-quality PW Doppler studies with sample volumes placed at or distal to the pulmonary valve or poorly aligned to the direction of RVOT flow were excluded. Similarly, patients with more than moderate valvular heart disease, known history of PE, established chronic thromboembolic pulmonary hypertension, and preexisting pulmonary hypertension, regardless of etiology, were excluded from this study.

Imaging

Contrast-enhanced computed tomographic scans were performed on multidetector Toshiba 64-slice scanners (Toshiba Medical Systems, Tokyo, Japan) using a standardized PE timing protocol adopted across our hospital systems. Contrast dye used was Isovue 300 or Isovue 370 (Bracco, Milan, Italy), tailored to the patient's renal function. RV strain, dilation, or dysfunction was deemed present if four-chamber RV diameter divided by left ventricular diameter was > 0.9 on CTA. The diagnosis of PE was confirmed when thromboemboli were visualized in an at least segmental pulmonary artery on contrast-enhanced multidetector computed tomography. Patients with PE were stratified according to definitions recommended by the American Heart Association scientific statement, published in 2011.[3] MPE was defined as acute PE with sustained hypotension (systolic blood pressure < 90 mm Hg for ≥15 min or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate < 40 beats/min with signs or symptoms of shock). SMPE was defined as acute PE without systemic hypotension (systolic blood pressure ≥ 90 mm Hg) but with RV dilation, defined as RV diameter divided by left ventricular diameter > 0.9 on CTA (in the four-chamber view). SSPE was defined as acute PE and the absence of clinical markers of adverse prognosis that define MPE or SMPE.

Echocardiographic variables for all patients were analyzed from transthoracic echocardiograms obtained with the Philips iE33, Cx-50, and EPIQ (Philips Medical Systems, Andover, MA) or the GE E9 Ultrasound (GE Medical Systems, Milwaukee, WI) systems. PW Doppler interrogation of the RVOT was performed from the parasternal short-axis view at the level of the aortic valve or from the subcostal short-axis view, with the sample volume placed approximately 0.5 cm proximal to the pulmonic valve. The "early systolic notching" (ESN) pattern (spike and dome morphology) was visually assessed and deemed present if the Doppler envelope exhibited a narrow peaked initial wave (spike) with early deceleration of the RVOT envelope producing a sharp notch within the first half of systole (i.e., notch location within the initial 50% of ejection, as estimated using the online time-caliper tool), followed by a second Doppler wave (dome) that was more curvilinear in appearance (Figure 1). Similarly, midsystolic notching was defined as a distinct notch falling within the second half of the systolic ejection period or, if the nadir occurred closer to the end of ejection, dividing the flow profile into two distinct peaks. Notch morphology was best appreciated when the Doppler beam was aligned parallel to RVOT outflow, with the PW sample volume placed at the appropriate location at sweep speeds of 50 to 100 mm/sec. (See additional illustrative case examples shown in Figures 1-3.) Care must be exercised not to conflate the "opening click" of the pulmonic valve with the systolic notch, a scenario that can occur if the PW sample gate is placed too close to the pulmonic valve.

Ejection time was measured in milliseconds from the beginning to the end of the RVOT Doppler envelope. Acceleration time (AT) was measured in milliseconds as the time to peak velocity of the RVOT envelope measured from the beginning of ejection. At least 3 cardiac cycles were measured and averaged for analysis. Deceleration Time was measured from the peak Doppler velocity to the end of ejection. Acceleration and Deceleration slopes were estimated by deploying the online slope tool using the same time points described for respective time measurements. Spike (S) and Dome (D) velocities were measured as the peak Doppler velocities of these waveforms, respectively. The AT/ejection time ratio was derived from values listed above. Notch time represents the duration of the Doppler notch

HIGHLIGHTS

- ESN reliably identified patients with MPE/SMPE but not those with SSPE
- ESN demonstrated superior predictive ability with a high negative predictive value
- Future prospective study to ascertain diagnostic utility in a broader population is warranted

measured in milliseconds, as shown in Figure 1. RVOT Doppler velocity-time integral was obtained in the standard manner by tracing the systolic RVOT PW Doppler envelope. RV size was measured as the basal RV dimension in the four-chamber apical view. The 60/60 sign was deemed present if RVOT AT was < 60 msec in the presence of a tricuspid peak systolic gradient > 30 mm Hg but < 60 mm Hg.[8] Regional pattern of RV dysfunction consistent with McConnell's sign was defined as akinesia of the mid free wall visualized along with preserved apical contractility.[9] All other variables were obtained in accordance with current American Society of Echocardiography guidelines.[10]

To assess interobserver variability, two authors (A.S. and Mo.S.) who were blinded to the PE diagnoses of these patients independently reviewed their echocardiograms for the presence of ESN in a total of 30 randomly selected samples, and agreement between the two authors was analyzed using the κ coefficient.

Statistical Analysis

Baseline characteristics were compared among the three groups using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Thereafter, we evaluated the utility of the spike-and-dome pattern in three steps. First, using CTA-confirmed diagnosis of MPE or SMPE as the gold standard, we evaluated the utility of the spike-and-dome pattern in diagnosing MPE or SMPE using probability statistics and receiver operating characteristic (ROC) curve analysis. Second, we evaluated similar diagnostic utility for prespecified echocardiographic variables, including notch-related parameters, RV dilation, and tricuspid regurgitation velocity. Optimal cutoffs for these echocardiographic parameters were derived as the values that minimized the square of the difference between sensitivity and specificity. The diagnostic performance of these parameters was then assessed using probability statistics and ROC analysis. Third, we identified parameters with potential incremental benefit over the spike-and-dome pattern using a model-based approach that retained the indicator for spike and dome in the model while selecting other variables using a backward stepwise selection iteration (P for inclusion = .10, P for exclusion = .20). The incremental benefit of combining the finally selected parameters to the spike-and-dome pattern were then evaluated using ROC analysis and probability statistics.

Secondary analysis for predictive utility of the spike-and-dome pattern for SSPE was performed after excluding patients with MPE or SMPE.

All analyses were performed using Stata version 14 (StataCorp, College Station, TX) with a two-tailed α value of 0.05.

RESULTS

A total of 5,152 patients underwent computed tomographic scans for suspected PE, of whom 526 (10.2%) had positive results for PE

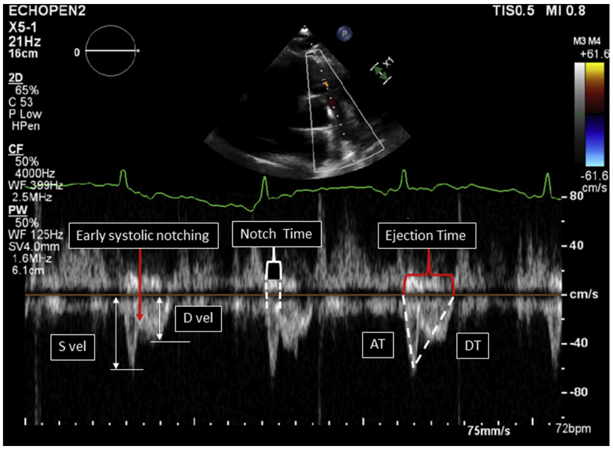

Figure 1 RVOT Doppler tracing in a patient with MPE, illustrating the characteristic ESN pattern and measurement methodology used for various other Doppler parameters analyzed in this study. *DT*, Deceleration time; *D vel*, dome velocity; *S vel*, spike velocity.

(including MPE or SMPE and SSPE). After initial screening criteria (no echocardiogram available or echocardiogram available but outside the prespecified 48-hour window, history of embolism, or pulmonary hypertension), a total of 260 patients from this group were short-listed for further analysis. Upon further screening and application of exclusion criteria (limited studies, RVOT PW Doppler data not recorded, or Doppler data recorded but technically inadequate for interpretation moderate or greater valvular disease), a total of 187 patients with PE qualified and were included in the final analysis. The reference group included a total of 90 patients without PE who met our selection criteria. In summary, a total of 277 patients (mean age 56 ± 16 years; 48% men; 100 [44%] with MPE or SMPE, 87 [38%] with SSPE, and 90 [39%] without PE) were studied. Differences in baseline characteristics and hemodynamics among the three groups are presented in Table 1, and details of various echocardiographic parameters evaluated in this study are presented in Table 2.

ESN was observed in 92% of patients with MPE or SMPE, 2% of those with SSPE, and in no patients without PE. There was good interobserver agreement in the identification of ESN, with 96.7% agreement (κ = 0.93, P < .001). Among patients with SSPE, systolic notching was predominantly midsystolic (19%) and less likely early systolic (2%). However, among patients with MPE or SMPE, systolic notching was predominantly early systolic (92%) and less likely midsystolic (1%). No systolic notching was observed in all control subjects (100%), 79% of patients with SSPE, and 7% of patients with MPE or SMPE. No unique characteristics were identified in the seven patients with MPE or SMPE who did not have the early notching pattern; of these, five patients had intermittent, poorly discernible ESN or midsystolic notching, and two patients had a characteristic triphasic Doppler pattern (see Figures 2B and 3B). The precise underlying mechanism for the triphasic pattern is unclear at this time.

Identification of the ESN pattern on echocardiography demonstrated good to excellent predictive ability for MPE or SMPE, with sensitivity of 92% (95% CI, 84%–97%), specificity of 99% (95% CI, 96%–100%), positive predictive value of 98% (95% CI, 91%–100%), negative predictive value of 96% (95% CI, 92%–98%), and area under the ROC curve of 0.96 (95% CI, 0.92–0.98), which

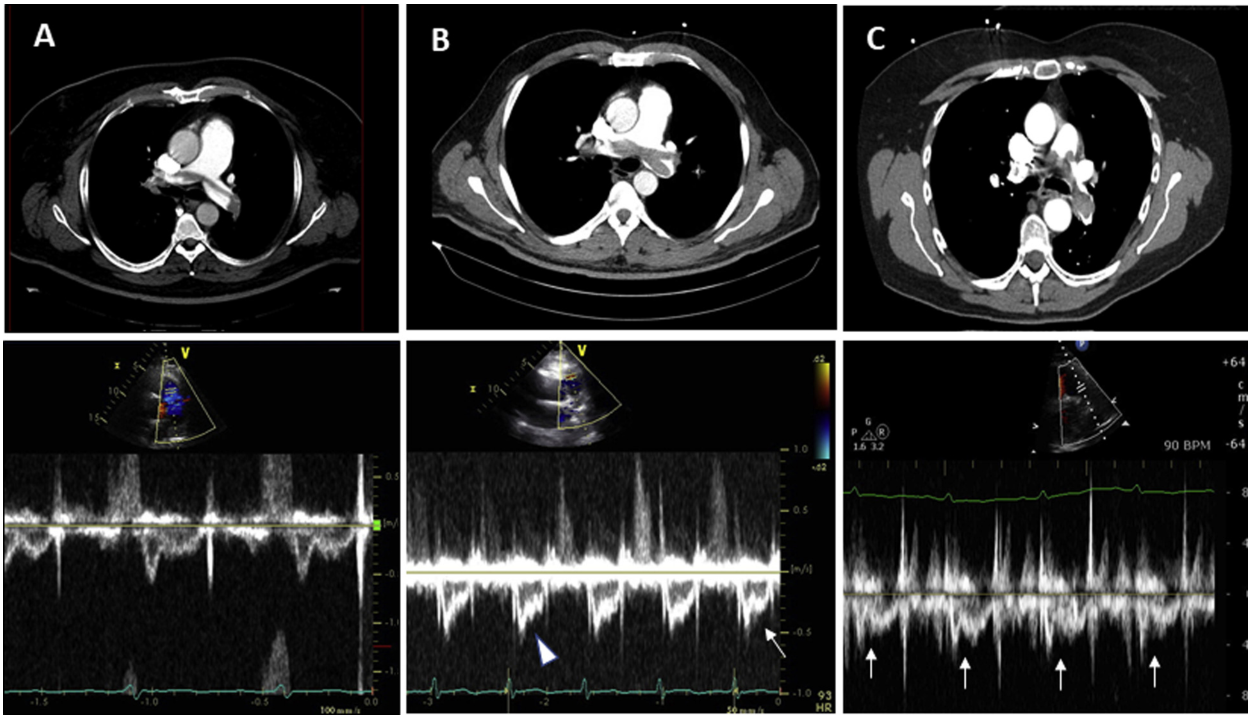

Figure 2 Illustrative case examples of SMPE showing representative computed tomographic angiographic images and corresponding RVOT Doppler patterns. **(A)** Saddle embolism with thrombus extension into branch pulmonary arteries and clear early notching pattern (sweep at 100 mm/sec). **(B)** Saddle embolism with large thrombus burden; note early notching *(white arrow)* and intermittent triphasic notching pattern *(white arrowhead)*. **(C)** Extensive thrombus in left main pulmonary artery showing early notching *(white arrows)*. Doppler patterns in **(B)** and **(C)** were recorded at 50 mm/sec.

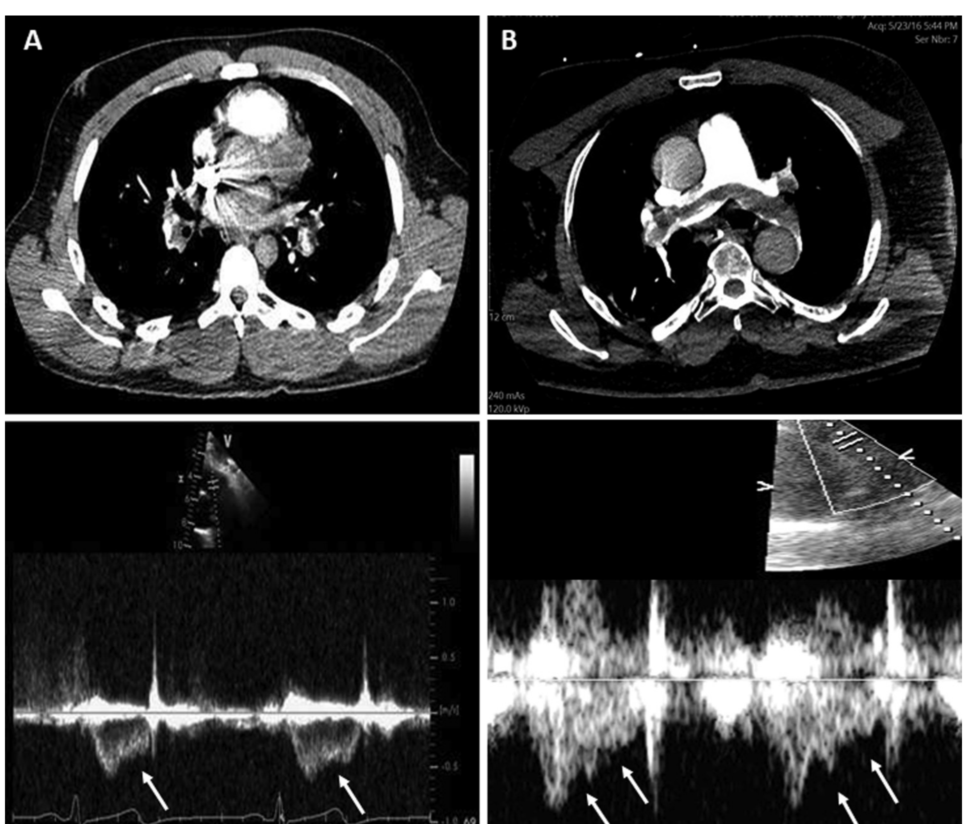

Figure 3 Additional case examples. **(A)** Midsystolic notching in a patient with SSPE and thrombi in branches of the right and left main pulmonary arteries. **(B)** Triphasic Doppler pattern in a patient with SMPE and saddle embolism. *Arrows* denote the locations of notches along the RVOT Doppler envelope.

Table 1 Baseline descriptive demographic, clinical, and hemodynamic characteristics of entire cohort

Variable	No PE (n = 90)	SSPE (n = 87)	MPE/SMPE (n = 100)	P
Age (y)	56 ± 13	56 ± 15	55 ± 14	.82
Male	51	36	56	.01
Black race	72	77	76	.06
Smoker	20	25	36	.04
Hypertension	77	61	57	.01
Diabetes	36	23	33	.13
COPD	16	17	10	.22
Malignancy	12	19	16	.50
SBP (mm Hg)	135 ± 23	127 ± 25	115 ± 33	.03
DBP (mm Hg)	76 ± 14	76 ± 14	74 ± 19	.45
Pulse rate (beats/min)	80 ± 19	99 ± 18	106 ± 19	<.001

COPD, Chronic obstructive pulmonary disease; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.
Data are expressed as mean ± SD or as percentages.

when compared side by side with the widely recognized McConnell's sign suggests superior predictive ability (Table 3). Notably, McConnell's sign assessment in this study yielded sensitivity of 52% (95% CI, 40%–63%), specificity of 97% (95% CI, 94%–99%), positive predictive value of 90% (95% CI, 77%–97%), negative predictive value of 82% (95% CI, 76%–87%), and area under the ROC curve of 0.75 (95% CI, 0.68–0.80) while the 60/60 sign yielded values of 51% (95% CI, 40%–62%), 96% (95% CI, 91%–99%), 93% (95% CI, 81%–99%), 70% (95% CI, 61%–77%), and 0.74 (95% CI, 0.68–0.79), respectively.

Notably, the addition of other echocardiographic parameters (Table 2) to the ESN pattern did not show any significant incremental benefit. In secondary analysis, the ESN pattern performed poorly for SSPE (Table 4).

DISCUSSION

In the present study, an ESN pattern of the RVOT Doppler envelope was a frequently observed finding in patients with MPE or SSPE, selected from among a cohort of individuals undergoing CTA for suspected PE. Despite promising diagnostic performance data compared with existing echocardiographic variables, in a select population of patients that excluded individuals with preexisting pulmonary arterial hypertension, the diagnostic accuracy of this sign, including its sensitivity and specificity, will need to be validated in a broader population of patients with less stringent exclusion criteria before it can be recommended for use in the clinical setting.

Echocardiography has traditionally been relegated to a supportive role in the evaluation of patients with suspected PE and used primarily to assess RV size and function in hemodynamically unstable patients.[11] Several echocardiographic parameters described in the literature, including McConnell's sign (reduced RV free wall contractility with preserved RV apical function), the 60/60 sign (AT < 60 msec in the presence of a tricuspid peak gradient > 30 mm Hg but < 60 mm Hg), paradoxical septal motion, and RV dilation can be helpful but lack the desired sensitivity, specificity, or negative predictive value (reported to be about 40%–50%) to be incorporated as first-line options in evaluation algorithms for suspected PE.[4-6,8,9,12,13] Our study findings on the diagnostic performance of the aforementioned echocardiographic variables are in accord with the published literature. Nonetheless, as an exception, it should be acknowledged that echocardiographically visualized right atrial thrombi, reported in <4% of unselected patients with PE, are notoriously associated with hemodynamic compromise and a poor prognosis.[14]

Our observations suggest that the simple visual assessment of RVOT Doppler morphology offers potentially insightful information on the coupling dynamics between the right ventricle and the pulmonary vasculature. Early studies describe a notching pattern of the RVOT Doppler envelope and transient midsystolic notching of the pulmonary valve (M mode), representing systolic flow deceleration in the RVOT from reflected waves in patients with pulmonary hypertension.[15,16] Subsequently, Torbicki *et al.*[17] reported short AT and ESN in a patient with acute MPE and appropriately attributed the restoration of flow in midsystole to the distal runoff of blood across the remaining patent pulmonary bed. Although there has been renewed interest in examining the significance of notching patterns in patients with chronic pulmonary arterial hypertension,[18] expanding previously reported literature on Doppler-hemodynamic correlations in this population,[19-22] data on the utility of RVOT Doppler systolic notching in the context of acute PE are sparse.[20]

The degree and timing of arterial wave reflection are determined in aggregate by pulmonary vascular resistance (PVR), reflected wave speed (determined by large and medium vessel stiffness), and the distance of the reflecting sites from the RVOT.[18,19,21] Conceptually, the short ATs and ESN pattern characteristic of the "spike and dome" observed in our cohort of patients with MPE or SMPE reflect the proximity of the increased after load to the RVOT and the markedly elevated PVR; this is in contrast to the midsystolic notching or late systolic notching pattern apparent with less severe grades of chronic precapillary pulmonary hypertension.[17,19] Of note, "systolic notching" is characteristically not observed in the subset patients with postcapillary or left-sided pulmonary venous hypertension, who by definition have normal PVR.[19] In aggregate, notching is strongly correlated with PVR (RV afterload) but may be dissociated from pulmonary artery pressure in patients with acute PE,[20] an observation mirrored in our cohort of patients with MPE or SMPE. Our findings demonstrating the ability to identify patients with extremely elevated PVR (MPE or SMPE) are also thematically in agreement with earlier observations suggesting that the combined presence of a short RVOT Doppler AT and low tricuspid velocity peak gradient may help discern acute PE from an assorted population of patients with chronic precapillary pulmonary hypertension.[19] Importantly, we also observed a weak correlation between pulmonary artery systolic pressure and notch timing in this study. These variables were inversely related but weakly correlated (correlation coefficient = −0.22). This observation likely stems from the fact that pulmonary artery systolic pressure, in the setting of "acute" hemodynamically significant PE, may be normal or even subnormal, reflecting the abrupt, precipitous decline in RV systolic performance (from RV stunning), although pulmonary artery systolic pressure often rises rapidly in the days following MPE or SMPE.

Contrast CTA remains the diagnostic modality of choice for the diagnosis of PE, given its high spatial and temporal resolution and the ability to visualize segmental and subsegmental arteries.[4] Although both tests (CTA and ventilation-perfusion scanning) are reliable and comparable[4] in terms of sensitivity and negative predictive value, a time-trend analysis report revealed that the widespread adoption of CTA in 1998 for diagnosing PE led to a sharp rise in PE incidence (an 80% increase from 1998 to 2006), without an

Table 2 Echocardiographic parameters in various study groups

Variable	No PE (n = 90)	SSPE (n = 87)	MPE/SMPE (n = 100)	P
RVOT ESN	0	2.0	92	<.001
AT (msec)	149 ± 45	101 ± 38	60 ± 19	<.001
DT (msec)	186 ± 46	175 ± 57	219 ± 44	<.001
AT/ejection time ratio	0.46 ± 0.11	0.38 ± 0.13	0.22 ± 0.07	<.001
Acceleration slope (cm/sec^2)	574 ± 255	945 ± 528	1,329 ± 545	<.001
Deceleration slope (cm/sec^2)	319 ± 136	393 ± 222	219 ± 84	<.001
RV basal diameter (cm)	3.4 ± 0.44	3.6 ± 0.52	4.4 ± 0.74	<.001
Slope ratio (acceleration slope/deceleration slope)	2.0 ± 1.0	3.0 ± 2.1	6.5 ± 2.5	<.001
Notch characteristics*				
NT (msec)	—	142 ± 29	106 ± 32	<.001
NT/ejection time	—	0.51 ± 0.11	0.39 ± 0.11	<.001
NT/RVOT VTI	—	13 ± 5.5	10 ± 3.3	<.001
S/D ratio (peak spike-and-dome velocity ratio)	—	1.5 ± 0.25	1.6 ± 0.26	.07
No notching	100	79	7	<.01
TR peak velocity (m/sec)	2.4 ± 0.56	2.8 ± 0.62	3.1 ± 0.60	<.001
60/60 sign	0	7.0	51	<.001
McConnell sign	0	7.1	52	<.001

DT, Deceleration time; *NT*, notch time; *TR*, tricuspid regurgitation; *VTI*, velocity-time integral.
Data are expressed as percentages or as mean ± SD.
*Among patients with SSPE, systolic notching was predominantly midsystolic (19%) and less likely early systolic (2%). However, among patients with MPE or SMPE, systolic notching was predominantly early systolic (92%) and less likely midsystolic (1%).

Table 3 Probability statistics of MPE or SMPE in the full cohort

Variable	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	AUROC
60/60 sign*	51 (40–62)	96 (91–99)	93 (81–99)	70 (61–77)	0.74 (0.68–0.79)
McConnell's sign	52 (40–63)	97 (94–99)	90 (77–97)	82 (76–87)	0.75 (0.68–0.80)
ESN pattern	92 (84–97)	99 (96–100)	98 (91–100)	96 (92–98)	0.96 (0.92–0.98)
AT ≤ 87msec	91 (83–94)	77 (70–83)	60 (52–69)	91 (88–94)	0.84 (0.79–0.88)
AT/ejection time ratio ≤ 0.38	90 (84–94)	59 (51–66)	54 (46–62)	91 (86–95)	0.77 (0.73–0.82)
DT ≥ 200 msec	64 (53–73)	70 (63–76)	49 (39–58)	81 (74–87)	0.67 (0.61–0.73)
DT/AT ratio ≥ 2.36	83 (74–90)	79 (71–83)	67 (57–75)	90 (85–93)	0.80 (0.76–0.85)
Acceleration slope ≥ 810 cm/sec^2	89 (80–94)	67 (60–73)	53 (46–63)	91 (87–96)	0.78 (0.73–0.81)
Deceleration slope ≤ 232 cm/sec^2	66 (55–76)	74 (67–79)	53 (43–62)	83 (76–88)	0.70 (0.64–0.75)
Slope ratio ≥ 4 (S/D)	81 (72–89)	83 (79–88)	73 (63–81)	90 (85–93)	0.83 (0.80–0.86)

AUROC, Area under the ROC curve; *DT*, deceleration time.
*Tricuspid regurgitation velocity < 3.9 m/sec plus pulmonary artery AT < 60 msec.

Table 4 Probability statistics for SSPE

Variable	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	AUROC
60/60 sign	7.0 (1.5–19)	94 (90–99)	92 (48–99)	48 (38–70)	0.51 (0.47–0.57)
McConnell sign	7.1 (2.6–13)	95 (90–99)	94 (59–99)	49 (42–56)	0.53 (0.51–0.55)
ESN	2.3 (0.24–7.4)	92 (86–99)	94 (15–99)	50 (43–57)	0.51 (0.49–0.52)

AUROC, Area under the ROC curve.

appreciable change in PE-related mortality. Collectively, these observations, including a declining PE case-fatality rate (in-hospital deaths among patients with diagnoses of PE) seem to reflect an increased detection or "overdiagnosis" of clinically insignificant, small or subsegmental pulmonary emboli.[23,24] Although the lethality of MPE and SMPE is widely recognized,[4,25] the clinical significance of isolated SSPE (on the basis of a large meta-analysis), found in roughly 9.4% of individuals with suspected PE, undergoing multidetector CTA is relatively less concerning, presumably because of the low 3-month thromboembolic risk of approximately 1%.[26] Along these lines, caution is also advised in interpreting the significance of small vascular defects on CTA, given the high false-positive rate (secondary to motion and technical artifacts), the low positive predictive value, and concerning levels of interobserver agreement.[26-28] Although the large majority of clinicians would likely pursue anticoagulation of patients with SSPE, it has been reported that the short-term risk of recurrent thromboembolism may be lower than the risk for adverse events ensuing from anticoagulation in such patients.[4,23] Accordingly, withholding anticoagulation in selected patients with SSPE may be reasonable given the very low risk for recurrent or fatal PE.[27] However, as reiterated in the 2014 European Society of Cardiology guidelines, it might be prudent to rule out deep vein thrombosis before opting to withhold anticoagulation in such patients.[4] In this context, the suboptimal performance and low diagnostic accuracy of our study's echocardiographic variables for SSPE may be viewed as desirable, essentially serving as an inherent filter to reliably and selectively isolate the subset of patients with MPE and SMPE from individuals undergoing workup for suspected PE.

A few limitations need to be acknowledged. First, we excluded patients with known pulmonary hypertension from the study. Hence, our findings may not be applicable to such groups of patients. The current evaluation was done in a single cohort and reflects a "best-case" scenario for test performance, and as such, our observations are not representative of the entire population of patients presenting with symptoms of PE. It is quite likely that our findings would have lower specificity when applied to a broader, less selected population that included patients with pulmonary arterial hypertension, acute hypoxic respiratory failure and other entities with elevated PVR. Accordingly, although further prospective study in additional cohorts is warranted, such clinical scenarios emphasize the unique value of CTA as a diagnostic tool in patients with suspected PE. Our study lacked invasive hemodynamic correlation, but we remain confident in the adoption of CTA alone as the gold standard for our analysis. Although speculative and in need of additional validation in a less selected population, early notching in patients with computed tomography–confirmed PE could potentially help identify a subset of patients with more severe pulmonary vascular obstruction at risk for greater hemodynamic compromise. It must be borne in mind that the RVOT Doppler early notching pattern is not specific for MPE or SMPE but is a highly specific sign of significantly elevated PVR. This hypothesis was elegantly demonstrated in experimental dog models following acute proximal PE and pulmonary artery banding.[29] Not surprisingly, we incidentally observed (unpublished data) a few instances of the early notching (spike-and-dome) pattern in individuals with very advanced pulmonary arterial hypertension and in patients with proximal obliteration or compression of one of the major pulmonary arteries from advanced lung cancer. Mid- or late systolic notching, on the other hand, is commonly observed in the vast majority of patients with precapillary pulmonary arterial hypertension. Regardless of the underlying mechanism, the finding of early notching, when identified for the first time, is abnormal and should prompt a workup for PE, pulmonary artery compression, or pulmonary arterial hypertension with CTA or a ventilation-perfusion scan and, when appropriate, with right heart catheterization to estimate PVR.

Notably, the low positivity rate for CTA, reported as 9% to 14% in the published literature (10.2% in our study),[30,31] frames the contemporary use of CTA, as a screening, inasmuch as a valuable diagnostic tool, while also implicitly underscoring the pressing need to develop more cost-effective screening strategies.[32-34]

Until such time as additional validation data are accrued, echocardiography (including the presence of ESN) should not be viewed as the primary screening test or a gatekeeper for CTA in the diagnosis of acute PE.

CONCLUSION

In patients with suspected acute PE, the pulmonary Doppler flow pattern of ESN has potential clinical utility for the detection of MPE or SMPE. Future prospective study to better establish its role in the management of acute PE is warranted.

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