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Diagnostic value of resting tricuspid regurgitation velocity and right ventricular ejection flow parameters for the detection of exercise induced pulmonary arterial hypertension

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Abstract

Our objectives were to evaluate resting tricuspid regurgitation velocity (TRV) and right ventricular outflow tract velocity curve ($RVOT_{vc}$) profiles as markers for development of exercise induced pulmonary arterial hypertension (ExPHT). ExPHT is an elusive cause of dyspnea and fatigue. When present, Doppler echocardiography can detect and quantify elevated pulmonary pressure. However, the characteristics and diagnostic value of resting TRV and $RVOT_{vc}$ indices in patients with ExPHT have not been fully addressed. The study population consisted of 52 subjects (mean age 40.5 ± 10.9, range 22–68 years) and was divided into three subsets as follows: 1. Patients (n = 22) with overt pulmonary hypertension (PHT), 2. Patients (n = 8) with ExPHT, 3. Healthy, asymptomatic volunteers (n = 22). $RVOT_{vc}$ indices included: Mean and peak velocity, systolic velocity time integral (VTI); velocity time integral at peak velocity (VTI_{max}), acceleration time; ejection time. TRV was used as an index of pulmonary artery systolic pressure. There were significant differences between normals and ExPHT for TRV, acceleration time, VTI_{Vmax}. TRV and VTI_{max} were predictive of EXPHT in a logistic regression model. *Conclusion*: (1) Patients with ExPHT have distinct Doppler velocity patterns suggesting the presence of a compromised pulmonary vascular bed even with normal pulmonary pressure at rest. (2) TRV and $RVOT_{vc}$ indices have potential diagnostic value in the early detection of ExPHT.

Abbreviations: AT/ET – Ratio of acceleration time to ejection time; ExPHT – Exercise induced pulmonary arterial hypertension; PHT – Pulmonary arterial hypertension; $RVOT_{vc}$ – Right ventricular outflow tract velocity curve; TRV – Tricuspid regurgitation velocity; VTI – Velocity time integral; VTI_{Vmax} – Velocity time integral at peak velocity

Introduction

Because of the non-specific nature of the symptoms and signs, pulmonary arterial hypertension (PHT) is often not diagnosed until in its late stage [1, 2]. Several studies have demonstrated the reliability of Doppler echocardiography to detect elevated pulmonary arterial pressure at rest [3–9] and with exercise [10–14]. The diagnostic utility of resting tricuspid regurgitation velocity (TRV) and pulsed Doppler right ventricular outflow tract velocity curve ($RVOT_{vc}$) indices to identify patients with occult or exercise induced PHT (ExPHT) has not been fully addressed [15]. The purpose of this study was to compare resting TRV and $RVOT_{vc}$ parameters in subjects with ExPHT, patients with overt PHT and normal controls in an effort to define Doppler markers of ExPHT.

Methods

Study population

The study population consisted of 52 subjects (mean age 40.5 ± 10.9, range 22–68 years; 22 men, 30 women) and comprised three groups:

I) Patients (n = 22) with documented PHT, mean age 42.6 ± 12.5 years (range 23–68), seven men, 15 women. There were seven patients with thromboembolic PHT and 15 with primary PHT.

II) Patients (n = 8) mean age 40.4 ± 12.6 years (range 20–54), three men, five women with ExPHT confirmed at the time of echo-Doppler bicycle exercise test.

III) Healthy, non smoking, active volunteers (n = 22) mean age 38.4 ± 8.3 years (range 21–53), 10 men, 12 women.

Groups I and II were consecutive patients referred to the pulmonary hypertension clinic to assess suspected or overt PHT. Symptomatic patients at rest or with ExPHT were age matched to controls for statistical comparisons.

Imaging protocol

All subjects underwent a standardized two-dimensional echocardiographic and Doppler examination at the time of referral to the PHT clinic. Specific views included parasternal long and short axis views, apical four and two chamber views and subcostal views. Pulsed and continuous wave Doppler profiles were recorded from all four cardiac valves. Subjects with ExPHT (Group I) underwent a two dimensional echocardiographic saline-enhanced Doppler exercise test to assess the tricuspid regurgitation velocity response to exercise as a correlate of the pulmonary systolic pressure [10, 11]. Symptom – limited exercise testing was performed with the use of a recumbent bicycle protocol individualized according to the cardiovascular and overall physical state of each subject.

The $RVOT_{vc}$ was recorded from the parasternal short axis view at the aortic valve level with the pulsed-wave Doppler sample volume positioned in the center of the right ventricular outflow tract just proximal the pulmonary valve. The area under the velocity curve was traced off-line. The $RVOT_{vc}$ flow parameters were calculated off line as mean of at least three consecutive beats and included: mean velocity, peak velocity, systolic VTI, VTI_{max}, acceleration and ejection times and their ratio (AT/ET) (Figure 1).

Statistical analysis

The three diagnostic groups (overt PHT, ExPHT, and normal controls) were compared using analysis of covariance (ANCOVA). Variables tested in this manner included TRV, mean and peak velocities, VTI, VTI_{max}, acceleration and ejection times and AT/ET. Pairwise comparisons of the three diagnostic groups were performed using Tukey's procedure. Second, we developed a diagnostic index for ExPH using a logistic regression model, with the outcome being exercise-induced ExPHT vs. controls (those with overt PHT were not considered). The variables significant in the ANCOVA model were included as initial covariates. Non-significant variables were excluded, and a final predictive model was obtained. Sensitivity, specificity, and positive predictive value of the model were calculated. All analyses were performed using SAS statistical software. Adjustments for heart rate were performed in all ANCOVA and logistic modeling

Results

Baseline patient characteristics

Mean ages across the groups did not differ after ANOVA testing ($p = 0.43$). Three patients (37.5%) had specific risk factors (systemic hypertension,

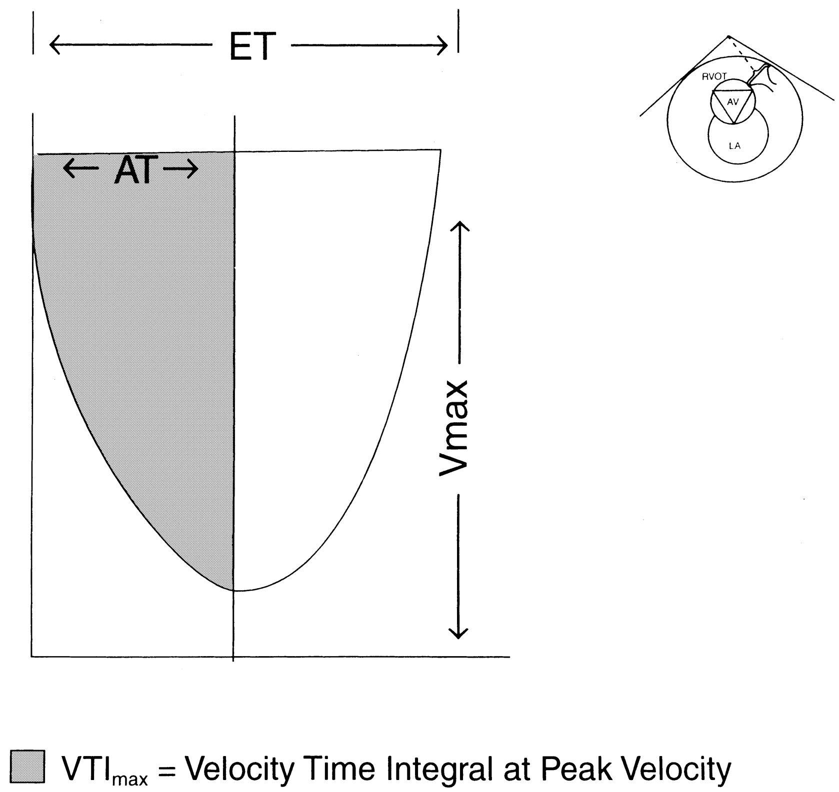

Figure 1. Schematic outline of right ventricular outflow tract velocity curve parameters.

obesity, lupus erythematosus, pulmonary emboli) associated with the development of primary or secondary PHT (Table 1). All eight patients were in sinus rhythm. Four patients (50%) had right axis deviation, three of whom also had incomplete right bundle branch block on standard 12-lead ECG.

Echocardiographic images were adequate for analysis in all eight patients with ExPHT. Major echocardiographic abnormalities included: right side enlargement (right atrium and/or ventricle) in three, left side abnormalities (atrial enlargement and left ventricular hypertrophy) in two. Four patients (50%) had normal two-dimensional echocardiograms (Table 1).

Exercise testing

The ExPHT group exercised to a workload of 126.9 ± 51.3 W, attaining a peak heart rate of 149.6 ± 27.6 beats/min, representing 82.4 ± 13.1% of age-predicted maximum. The peak rate-pressure product was 23,846 ± 6625. Four patients (50%) had a suboptimal heart rate response (< 85% age-predicted maximum). The TRV at peak exercise was 4.5 ± 0.8 with a range from 3.5 to 5.8 m/s. The exercise was terminated in all patients because of fatigue or dyspnea. Exercise variables for the patients with ExPHT are presented in Table 1.

Doppler findings

TRV and $RVOT_{vc}$ profiles were adequate for analysis in all subjects. Figure 2 is a composite of the $RVOT_{vc}$ for a normal volunteer, a patient with ExPHT and a patient with overt PHT.

The results of the ANCOVAs comparing the three diagnostic groups, adjusted for heart rate, showed five of the eight doppler variables analyzed (TRV, VTI, VTI_{max}, acceleration time, AT/ET)

Table 1. Resting and exercise parameters of patients with exercise induced pulmonary arterial hypertension

Resting									Exercise						
Pt	Age, sex	Risk factors	ECG	ECHO	O_2 sat (%)	Systemic BP (mmHg)	HR	TR (m/s)	Stage	Time (min)	Watts	O_2 sat (%)	Systemic BP (mmHg)	HR (%)	TR (m/s)
1	50, F	–	RAD, IRBBB	RAE, RVE, LAE	94	130/84	83	2.3	6	12	60	95	182/82	173 (100)	4.6
2	39, F	–	RAD	RVE, Mod. TR	97	121/64	52	2.3	3	6	100	99	141/75	109 (60)	3.5
3	54, M	Systemic HP	–	LVH	97	131/67	89	2.3	7	14	70	97	134/118	121 (72)	4.2
4	50, M	Obesity	–	–	96	151/75	76	1.7	7	14	175	95	178/100	125 (73)	5.1
5	22, M	–	RAD, IRBBB	RAE	97	136/76	99	2.4	4	11	160	98	156/99	180 (90)	5.1
6	20, M		–	–	99	147/91	103	2.5	8	16	200	99	191/94	174 (87)	5.8
7	41, F	LES PE	RAD, IRBBB	–	99	126/66	86	2.3	4	8	100	100	137/67	151 (84)	4.3
8	44, F		–	–	100	130/65	81	2.3	6	11	150	98	143/103	164 (93)	3.5

ECG = Electrocardiogram; BP = Systemic blood pressure; HR = Heart rate; TR = Tricuspid regurgitation peak velocity; HR (%) = Percent of maximum predicted HR; HP = Hypertension; LES = Lupus erythematosus systemic; PE = Pulmonary embolism; RAD = Right axis deviation; IRBBB = Incomplete right bundle brunch block; RAE = Right atrial enlargement; RVE = Right ventricular enlargement; LAE = Left atrial enlargement.

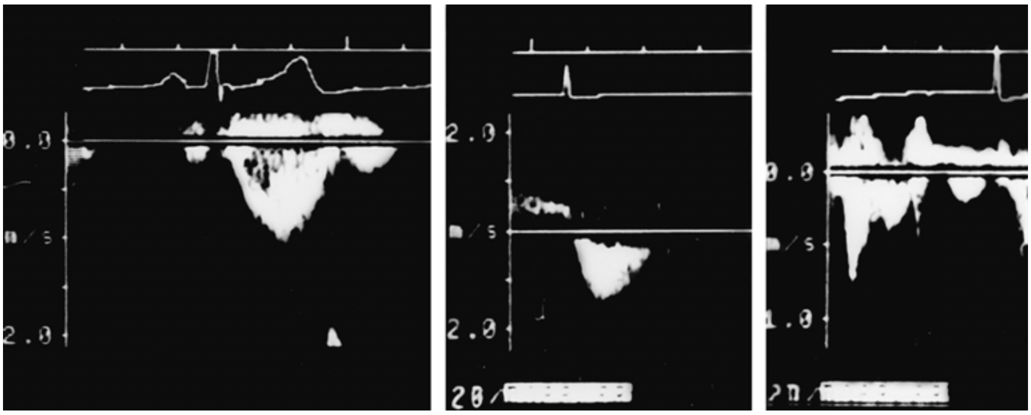

Figure 2. Comparison of pulmonary flow patterns among normal control (left), patient with exercise induced pulmonary artery hypertension (middle) and documented overt pulmonary arterial hypertension (right). A symmetric pattern is usually seen only in subjects with normal pulmonary artery pressure. An asymmetric pattern may be present in patients with ExPHT. A midsystolic notch is highly specific for patients with overt PHT.

Table 2. Analysis of Covariance (ANCOVA) and pairwise comparisons [in brackets, at $p < 0.05$, by *post-hoc* Tukey's method].

Variables	Group I (PHT) n = 22 Mean ± SD (range)	Group II (ExPHT) n = 8 Mean ± SD (range)	Group III (Controls) n = 22 Mean ± SD (range)	*p*-Value (overall) [sig. pairwise comparisons]
HR (beats/min)	82.4 ± 11.2 (67–117)	78.3 ± 13.1 (55–94)	68.0 ± 8.7 (59–88)	<0.0001
TRV (m/s)	4.3 ± 0.8 (2.9–6.2)	2.3 ± 0.25 (1.7–2.5)	1.9 ± 0.2 (1.3–2.4)	<0.0001 [I–II, I–III, II–III*]
$RVOT_{vc}$ indices				
MV (m/s)	0.4 7 ± 0.13 (0.27–0.88)	0.55 ± 0.20 (0.34–0.93)	0.51 ± 0.08 (0.37–0.68)	0.2556
PV (m/s)	0.79 ± 0.2 (0.49–1.43)	0.87 ± 0.27 (0.58–1.39)	0.82 ± 0.14 (0.58–1.10)	0.489
VTI (m)	0.15 ± 0.06 (0.06–0.33)	0.19 ± 0.06 (0.12–0.31)	0.20 ± 0.03 (0.13–0.27)	0.0238 [I–III]
VTI_{max} (m)	0.04 ± 0.02 (0.017–0.099)	0.07 ± 0.02 (0.03–0.10)	0.09 ± 0.01 (0.07–0.12)	<0.0001 [I–II, I–III, II–III]
AT (s)	0.08 ± 0.03 (0.03–0.15)	0.12 ± 0.04 (0.05–0.18)	0.17 ± 0.03 (0.11–0.23)	<0.0001 [I–II, I–III, II–III]
ET (s)	0.30 ± 0.09 (0.13–0.6)	0.34 ± 0.04 (0.27–0.41)	0.38 ± 0.06 (0.27–0.54)	0.1218
AT/ET	0.27 ± 0.11 (0.13–0.63)	0.36 ± 0.12 (0.16–0.52)	0.45 ± 0.05 (0.37–0.55)	<0.0001 [I–III]

* pairwise comparison significant by *t*-test.
HR = Heart rate; TRV = Tricuspid regurgitation velocity; $RVOT_{vc}$ = Right ventricular outflow tract velocity curve; MV = Mean velocity; PV = Peak velocity; VTI = Velocity time integral; VTI_{max} = Velocity time integral at peak velocity; AT = Acceleration time; ET = Ejection time; AT/ET = AT to ET ratio.

had significant group differences. Table 2 illustrates both overall significance and significant pairwise comparisons.

For TRV, normal subjects had the lowest values, with higher values for ExPHT and even higher values for overt PHT. VTI, VTI_{max}, acceleration time, AT/ET showed the reverse trend, with the highest values seen in normal subjects. For acceleration time and VTI_{max}, the ExPHT group had values midway between the normal controls and PHT groups, and all three groups were pairwise significantly different from each other. For VTI and AT/ET, the normal controls were significantly different from the overt PHT group, but the ExPH group was not significantly different from either. For TRV, the ExPH group had values similar to the normal controls, and both of these groups were significantly different from the overt PHT group but not significantly different from each other. However, the variance of the overt PHT group was much larger than the variance of the other two groups, and a distinct difference between the ExPHT group and normal subjects was evident in the box plots (Figure 3A). A *t*-test comparing these two groups was highly significant ($p = 0.001$).

The goal of finding a diagnostic index to predict ExPHT was addressed by considering only this group and the normal controls (i.e., excluding those with overt PHT). Logistic regression showed that higher values of TRV and lower values of VTI_{max} were predictive of ExPHT. No other variables were significant after adjusting for these two. The combination of strong effects and a small sample size led to odds ratios estimated to be close to infinite and zero, respectively. The sensitivity of the prediction,

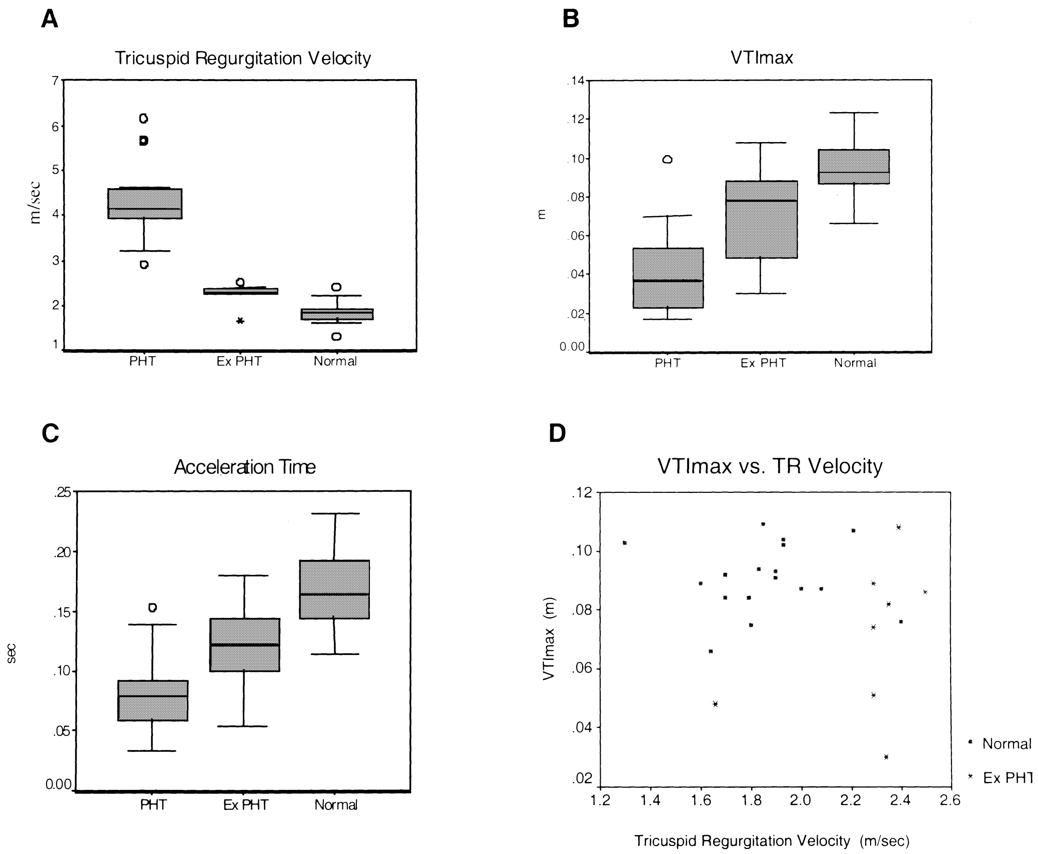

Figure 3. Distinct differences are evident for tricuspid regurgitation velocity (TRV) (A), velocity time integral at peak velocity (VTI_{max}) (B) and acceleration time (C) among the patients with overt pulmonary arterial hypertension (PHT), exercise induced pulmonary arterial hypertension (ExPHT) and normal controls, (D) demonstrated that a resting TRV of > 2.2 m/s and a $VTI_{max} < 0.07$ m may indicate patients at risk of exercise induced pulmonary arterial hypertension.

using a cut-off predictive probability of 0.5, was approximately 80%, and the specificity was 94%, with 96% of observations correctly classified. However, using TRV (greater than or less than 2.2 m/s) provides very good prediction. With this cut-off, sensitivity was 88% and specificity was 88%, with 85% of observations correctly classified. In addition, using VTI_{max} alone, a predictive model suggested a cut-point of 0.07, with patients having VTI_{max} less than 0.07 being more likely to ExPHT.

Discussion

Pulmonary arterial hypertension is a well recognized cause of non-specific symptoms such as dyspnea and fatigue [1, 2]. The diagnosis is often is made in its advanced stages due to the non-specific nature of the early symptoms and signs of this condition [1, 2]. Although clinical assessment is essential in the initial evaluation of these patients, echocardiography is a key screening tool in the diagnostic algorithm in patients with suspected PHT [2, 16, 17].

In addition to overt PHT, there is a subset of patients with ExPHT who have similar clinical symptoms but normal or near normal pulmonary pressure at rest [10, 13, 15, 18–20]. Identification of the underlying pathology in these patients has been difficult and usually requires measurement of pulmonary pressure with exercise [10, 15, 18–20].

Doppler echocardiography

Prior studies have demonstrated the reliability of Doppler echocardiography to detect elevated pulmonary arterial pressure at rest [3–9] and with exercise [10–13]. Both TRV and acceleration time have been shown to have linear (positive and negative respectively) correlations with pulmonary artery systolic and mean pressure respectively [3–9].

In the study presented here we have demonstrated that $RVOT_{vc}$ patterns have distinct characteristics among normal control, patients with ExPHT and documented overt PHT. Secondly the combination of TRV and VTI_{max} has a sensitivity of 88% and probability of correct categorization of 96% (cut-off point < 0.5) for detecting ExPHT. Prior studies have addressed this issue as well. Migueres et al. described significant changes in resting Doppler $RVOT_{vc}$ in patients with ExPHT [15]. These investigators noted that a time to peak velocity > 120 ms had a specificity of 98% for excluding ExPHT although a significant overlap was found for values between 100 and 120 ms. In their study the most reliable index to detect ExPHT was the right ventricular pre-ejection period to right ventricular ejection period ratio which showed a sensitivity of 85% and a specificity of 75% for values above 0.3 [15].

Limitations

Although 96% of patients were correctly predicted with this model, some caution is warranted. The sample size available was fairly small for generating a predictive model. Although TR and VTI_{max} appear to be highly predictive of ExPHT, the precise cut-points may require refinement by future studies. In addition, the high predictive value of VTI_{max} is primarily due to a single patient with low TRV but also low VTI_{max} (Figure 3D). We had no other patients with this combination of parameters to test whether this prediction will apply to other patients. However, the fact that in general, low values of VTI_{max} tend to predict patients with exercise-induced PHT lends credence to this prediction, even in the presence of a low TRV. We evaluated only patients with ExPHT identified in a specialized PHT clinic. As such our findings may not translate to the general population or different etiologies of PHT. Finally more information are warranted for the natural history of patients with ExPHT.

Clinical utility

Our results suggest that patients with clinical suspicion of ExPHT, with a resting TRV of > 2.2 m/s as the initial diagnostic indicator, followed by a $VTI_{max} < 0.07$ m, should be sent for an echo

Doppler exercise test that may unmask a latent or occult PHT.

Conclusion

Patients with ExPHT have distinct TRV and $RVOT_{vc}$ patterns suggesting a compromised vascular bed even with normal pulmonary artery systolic pressures at rest. TRV and VTI_{max} indices have potential diagnostic value in the early detection of ExPHT.

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