

# Validation of the isovolumetric relaxation time for the estimation of pulmonary systolic arterial blood pressure in chronic pulmonary hypertension

Inês Zimbarra Cabrita<sup>1\*</sup>, Cristina Ruísánchez<sup>2</sup>, Julia Grapsa<sup>1</sup>, David Dawson<sup>1</sup>, Bernard North<sup>3</sup>, Fausto J. Pinto<sup>4</sup>, J. Simon R. Gibbs<sup>5</sup>, and Petros Nihoyannopoulos<sup>1</sup>

<sup>1</sup>Department of Cardiovascular Sciences, Hammersmith Hospital, Imperial College NHS Trust, Du Cane Road, London W12 0HS, UK; <sup>2</sup>Hospital Universitario Marques de Valdecilla, Avda. Valdecilla no 25, Santander, Cantabria 39008, Spain; <sup>3</sup>Statistical Advisory Service, Imperial College London, 4th Floor, 8 Princes Gardens, London SW7 1NA, UK;

<sup>4</sup>Hospital Santa Maria, Lisbon Academic Medical Centre, Serv Cardiologia I, CCUL, Instituto Cardiovascular de Lisboa, Rua Tomás da Fonseca, F-P2 1600-209 Lisboa, Portugal; and

<sup>5</sup>National Pulmonary Hypertension Service, Department of Cardiology, Hammersmith Hospital, Imperial College NHS Trust, London W12 0HS, UK

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## Aims

Transthoracic echocardiography is a useful technique for non-invasive detection of pulmonary arterial systolic pressure (PASP). Isovolumic relaxation time (IVRT) measured by Doppler tissue imaging (DTI) is a sensitive measurement of changes in pulmonary vasculature. Our aim was to validate IVRT in the echocardiographic assessment of pulmonary hypertension (PH) patients.

## Methods and results

We studied 196 PH patients (67% women, mean age  $51.8 \pm 16.6$  years, mean PASP:  $81 \pm 24$  mmHg) and 37 consecutive age- and sex-matched controls (58% women, mean age  $44.7 \pm 16.4$  years, mean PASP  $27.7 \pm 5.5$  mmHg). The estimation of PASP was derived from tricuspid regurgitation velocity according to the Bernoulli equation. The measurement of IVRT was calculated using pulsed tissue Doppler. In the PH group and in the healthy volunteers group ( $P < 0.0001$ ), the average IVRT was  $113.4 \pm 28.5$  ms [95% confidence interval (CI): 109–117] and  $41 \pm 12.5$  ms (95% CI: 37–45), respectively. We found a strong correlation between IVRT and systolic pulmonary pressure in the PH group ( $r = 0.52$ ,  $P < 0.0001$ ) and a cut-off of 75 ms showed a sensitivity and specificity of 94% and 97%, respectively, for the prediction of elevated PASP.

## Conclusion

The determination of IVRT by DTI is a simple and reproducible method that correlates well with PASP. It is, therefore, a parameter to consider in the echocardiographic assessment of patients with PH, and may be particularly important when the tricuspid Doppler signal is poor.

## Keywords

Pulmonary hypertension • Isovolumic relaxation time • Doppler tissue imaging • Right ventricle

## Introduction

Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure (PAP) and impaired right ventricular (RV) function. The assessment of the PAP is of importance in the screening for disease and in its monitoring and prognosis, since persistent PH with right heart failure is related to a significant increased risk of death.<sup>1–3</sup> Transthoracic echocardiography is an

excellent method for non-invasive detection of pulmonary arterial systolic pressure (PASP), using the tricuspid regurgitation velocity (TRV) and the equation of Bernoulli.<sup>4–8</sup> However, this measurement depends on a good tricuspid regurgitation signal, which is not present in all patients.<sup>7,9–11</sup>

Pulsed Doppler tissue imaging (DTI) is a relatively new echocardiographic technique that provides information on the velocities and intervals from the myocardial wall. Typically,

\* Corresponding author. Tel: +44 20 8383 3948; fax: +44 20 8383 4392, Email: ines.cabrita05@imperial.ac.uk

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the signal is composed of DTI systolic wave (Sm), the waves of early and late diastolic filling (Em, Am), the isovolumetric relaxation time (IVRT), and isovolumetric contraction time (IVCT).<sup>12–14</sup>

The RV IVRT is the interval of time from the pulmonary valve closure to tricuspid valve opening. This parameter can be measured by DTI, and it is sensitive to changes in PAP and heart rate.<sup>15</sup> It has been demonstrated that IVRT correlates well with invasively measured PASP.<sup>16,17</sup>

Our aim was to analyse the relationship between IVRT and PASP non-invasively measured with echocardiography, and validate this parameter in the echocardiographic assessment of PH patients.

Methods

Participants

One hundred and ninety-six consecutive chronic PH patients, who were referred from the National Pulmonary Hypertension Service of our hospital between May 2005 and April 2007, were evaluated retrospectively. All patients underwent an echocardiographic study at the echocardiography laboratory of Hammersmith Hospital. Patients were diagnosed by right heart catheterization, with the mean PA pressure >25 mmHg, pulmonary vascular resistance more than 3 Wood units, and pulmonary capillary wedge pressure <15 mmHg, to exclude co-existing left ventricular failure.

Exclusion criteria were: incomplete data on echocardiogram, other rhythm than sinus rhythm, the presence of a pacemaker or defibrillator lead in the RV, severe tricuspid regurgitation,<sup>18</sup> complete right or left bundle branch block in order to avoid alterations in timings of the cardiac cycle due to conduction disturbances,<sup>19</sup> and patients with co-existent left heart disease (impairment of systolic or diastolic function and valvular disease) to avoid the possible influence of ventricular interaction.<sup>18,20,21</sup>

A second group of 37 consecutive age- and sex-matched healthy people with PASP <39 mmHg<sup>11</sup> was included as a control group.

The PASP was estimated by echocardiography based on TRV. The pressure gradient RV to the right atrium was calculated as  $4V^2$

according to Bernoulli's equation, where *V* is the peak velocity of the TR jet.<sup>3,4</sup> The PASP was estimated using the equation  $PASP = 4V^2 + RA$  pressure. The right arterial pressure (RAP) was derived from the inferior vena cava diameter and degree of respiratory collapse. The duration of IVRT was calculated using pulsed tissue Doppler of the lateral tricuspid annulus and was corrected for heart rate (IVRTc) according to the formula  $(IVRTc = IVRT/\sqrt{RR\%})$ . All measurements were derived from the mean of three consecutive cardiac cycles (Figure 1).

Echocardiography

Subjects were studied with ultrasound equipment (Philips Sonos 7500, transducer S3 1.8–3 MHz) equipped with DTI. An electrocardiogram was recorded simultaneously in all subjects. In all patients, qualitative estimation (composite score of RV impairment according to trabeculation, dilatation, hypertrophy, and contractility), RV peak systolic velocity (S-wave), and myocardial performance index (MPI) were used to assess RV function.

Conventional Doppler

In order to measure MPI by conventional pulsed Doppler, the sample was placed between the tips of the tricuspid leaflets in the four chambers' view and the 'a' interval was measured between cessation and onset of the tricuspid inflow. The RV inflow was studied placing the sample just below the pulmonary valve in the short-axis view and the 'b' interval was measured between onset and cessation of the RV outflow. The sum of isovolumic contraction time and isovolumic relaxation time was obtained by subtracting *b* from *a*. MPI was calculated as  $(a - b)/b$ . To account for variations in heart rate, mean values were obtained by averaging a minimum of three consecutive cardiac cycles. Doppler tracings were recorded with a sweep speed of 100 mm/s.

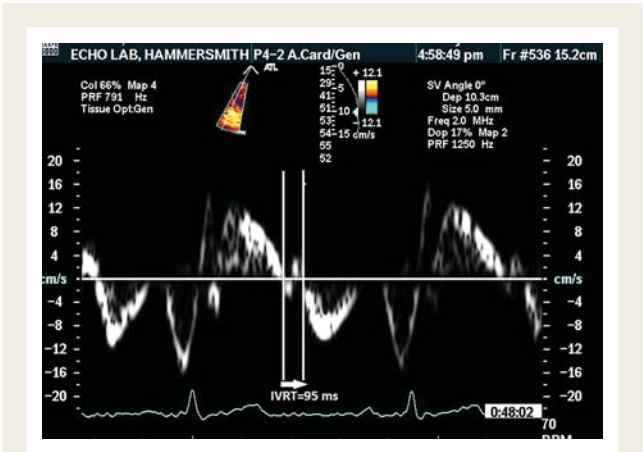
Doppler tissue imaging

Pulsed DTI data were obtained from a 2 mm sample volume placed at the lateral tricuspid annulus in the apical four-chamber view recorded during held end-expiration. The resulting velocities were recorded at a sweep speed of 100 mm/s and stored in digital format for later analysis (with ProSolv CardioVascular software). To account for variations in heart rate, three consecutive cycles were recorded and mean values were obtained. Isovolumic contraction time (tICT) was measured between cessation of A'-wave and onset of S-wave; DTI ejection time (tET) was obtained between onset and cessation of S-wave; DTI isovolumic relaxation time (tIVR) was obtained between cessation of S-wave and onset of E'-wave (Figure 1). Myocardial performance index (tMPI) was calculated as the sum of IVC time and isovolumic relaxation time divided by ejection time  $(tICT + tIVR)/(tET)$ . Special attention was paid to keep the best possible alignment between the tricuspid annulus motion and the ultrasound beam. Filters were set to exclude high-frequency signals. Gains were minimized to allow a clear tissue signal with minimal background noise. As IVRT is heart rate dependent, it was divided by RR time interval  $(IVRT/RR\%)$ .

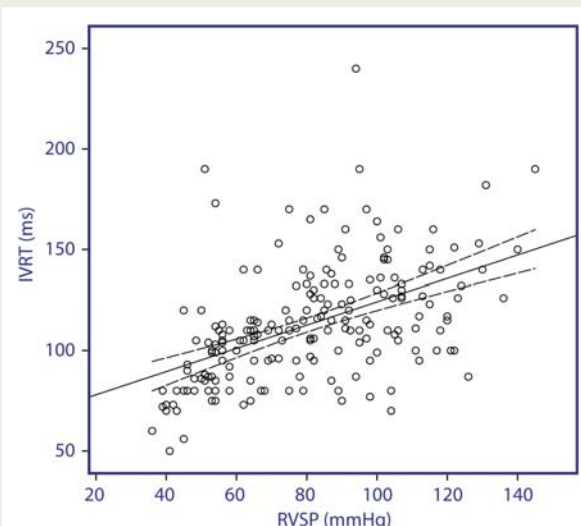
Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (IBM SPSS Statistics, USA) and MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium).

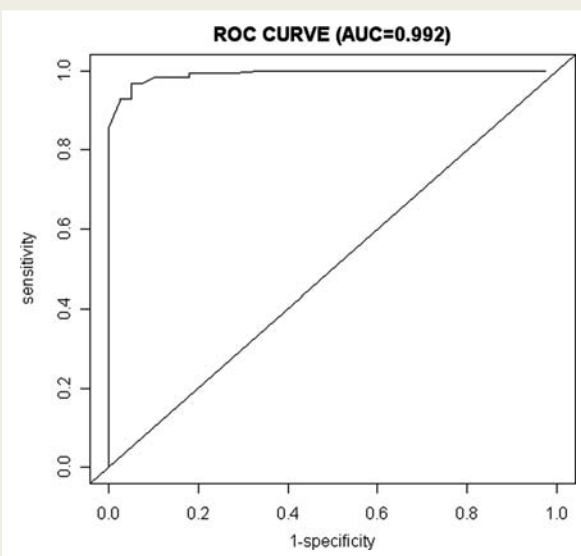
All data are expressed as mean value ± SD. Linear regression analysis was used to compare the pulsed Doppler with the TDI methods for the measurement of systolic and diastolic time intervals. Data were assessed for normality using the Kolmogorov–Smirnov test. Quantitative variables with a non-parametric distribution were compared between the groups using the Mann–Whitney *U*-test.



**Figure 1** Intervals measured from pulsed tissue Doppler obtained from the lateral tricuspid annulus. ICTt, tissue isovolumic contraction time; ETt, tissue ejection time; IVRTt, tissue isovolumic relaxation time.



**Figure 2** Correlation of IVRT with RV systolic pressure in the PH group ( $n = 196$ ).



**Figure 3** ROC curve for predicting  $\text{PASP} \geq 39$  mmHg. AUC: 0.992. (95% CI: 109–117). Sensitivity:  $9.278351 \times 10^{-1}$ , specificity:  $9.487179 \times 10^{-1}$ , odds ratio:  $4.454925 \times 10^{-3}$ ,  $P < 0.001$ .

Correlations were examined by Spearman's correlation model for non-parametric data. Estimates of the sensitivity and specificity of IVRT for predicting  $\text{PASP} \geq 39$  mmHg were assessed by constructing receiver-operating characteristics (ROC) curves. A  $P$ -value of  $< 0.05$  was considered to be statistically significant.

## Results

The studied cohort consisted of 196 patients with PH (67% women, mean age  $51 \pm 16$  years, mean  $\text{PASP}$ :  $81.4 \pm 24.7$  mmHg) and

**Table 1** Demographics and echocardiographic characteristics of the study population

Characteristics	$n$	PH group, mean (SD)/median (SD) <sup>a</sup>	$n$	No PH group, mean (SD)/median (SD) <sup>a</sup>
Sex (M/F)		65/131		16/21
Age (year)	196	$51.8 \pm 16.6$	37	$44.7 \pm 16.4^*$
Heart rate (bpm)	196	$76.5 \pm 14.9^a$	37	$71.2 \pm 11.2$
TRV (m/s)	196	$4.1 \pm 0.69$	37	$2.3 \pm 0.24^*$
RVSP (mmHg)	196	$81.4 \pm 24.7$	37	$27.7 \pm 5.5^*$
MPI	176	$0.68 \pm 0.21$	20	$0.24 \pm 0.07$
tMPI	196	$0.67 \pm 0.22^a$	37	$0.25 \pm 0.08^{a*}$
Sm (cm/s)	196	$10 \pm 2.5^a$	35	$14.3 \pm 2.3^*$
IVRT (ms)	196	$110.5 \pm 29.2^a$	37	$41.4 \pm 12.5^*$

IVRT, isovolumic relaxation time; MPI, myocardial performance index by pulsed Doppler; RVSP, right ventricular systolic pressure; Sm, peak systolic tissue Doppler velocity of the lateral tricuspid annulus; SD, standard deviation; tMPI, myocardial performance index by tissue Doppler; TRV, tricuspid regurgitant velocity. Values are mean (SD).

<sup>a</sup>Values are median (SD).

\* $P < 0.0001$ .

37 controls (58% women, mean age  $44.7 \pm 16.4$ , mean  $\text{PASP}$   $27 \pm 5.5$  mmHg). The aetiology of PH was PAH (111 patients), veno-occlusive disease (3 patients), lung disease (22 patients), chronic thromboembolic PH (54 patients), and PH with unclear/multifactorial mechanisms (6 patients).

The baseline characteristics of the study population are presented in Table 1.

There was a statistically significant difference in the duration of IVRT between the patients and healthy volunteers ( $P < 0.0001$ ). In the PH group and healthy subjects, the average of IVRT was  $113.4 \pm 28.5$  ms [95% confidence interval (CI): 109–117] and  $41 \pm 12.5$  ms (95% CI: 37–45), respectively.

We found a significant correlation between IVRT and  $\text{PASP}$  in the PH group ( $r = 0.50$ ,  $P < 0.0001$ ) which was improved with IVRT/RR% ( $r = 0.52$ ,  $P < 0.0001$ ) (Figure 2). IVRT and IVRT/RR% had a significant correlation both with MPI by DTI and pulsed Doppler (Table 2).

According to the physiological principle that RAP influences IVRT,<sup>22</sup> when patients with increased estimated mean RAP ( $\geq 15$  mmHg) were excluded, the correlation between  $\text{PASP}$  and IVRT was improved ( $r = 0.60$ ,  $P < 0.01$ ) and an inverse relation between IVRT and RAP was observed.

When only the healthy volunteers were taken into account, a significant correlation between IVRT and  $\text{PASP}$  was found ( $r = 0.37$ ,  $P = 0.02$ ). Furthermore, a stronger correlation was found with IVRT/RR% ( $r = 0.48$ ,  $P = 0.002$ ).

A cut-off of 75 ms IVRT showed a sensitivity and specificity of 94 and 97%, respectively, for the prediction of elevated  $\text{PASP}$  (as defined  $\text{PASP} \geq 39$  mmHg) (Figure 3).

## Reproducibility

No significant intra- and interobserver variability for the tricuspid lateral annulus tissue Doppler-derived MPI ( $a$  and  $b$  intervals) has

**Table 2** Correlations of IVRT with RVSP, myocardial performance index by tissue Doppler and pulsed Doppler and Sm wave (peak systolic tissue Doppler velocity of the lateral tricuspid annulus) in patients with PH

	RVSP (mmHg) (n = 196)	MPIt (n = 196)	MPI (n = 176)	Sm (cm/s) (n = 196)
IVRT (ms)	$r = 0.50$ , $P < 0.0001$	$r = 0.57$ , $P < 0.001$	$r = 0.41$ , $P < 0.001$	$r = -0.14$ , $P = 0.04$
IVRT/RR%	$r = 0.52$ , $P < 0.0001$	$r = 0.50$ , $P < 0.001$	$r = 0.43$ , $P < 0.001$	$r = -0.13$ , $P = 0.05$

MPI, myocardial performance index; Sm, peak systolic tissue Doppler velocity of the lateral tricuspid annulus; tMPI, myocardial performance index by tissue Doppler.

been shown previously in 50 consecutive PH patients of this cohort with the degree of RV systolic impairment and TRV blinded to the operators.<sup>23</sup>

Discussion

PAP can be estimated using Doppler echocardiography and several reports suggest that this method is appropriate in 75–80% of patients.<sup>24,25</sup> In the specific study, we investigated an alternative echocardiographic method for the estimation of increased PAPs. Right heart catheterization remains the gold standard technique for the measurement of PAP,<sup>26</sup> and it has been shown that tricuspid regurgitation peak pressure gradient correlates significantly with PASP after an accurate estimate of RAP.<sup>14,27</sup> Using phonocardiography and pulse tracings, Burstin, in 1967, shown that PASP could be estimated non-invasively by measuring the time interval between the pulmonary valve closure to the onset of tricuspid flow. DTI is a relatively new technique which provides the assessment of myocardial motion and time intervals throughout the cardiac cycle.<sup>28–30</sup> Several studies have shown the use of IVRT measured by DTI at the lateral tricuspid annulus to distinguish patients with increased PASP.<sup>15,31</sup>

A significant correlation of IVRT with the measurement of invasive PASP has been demonstrated.<sup>15,16,17,32</sup> Abbas et al.<sup>22</sup> demonstrated an inverse relationship between IVRT and RAP, with 80% sensitivity and 87.7% specificity for IVRT < 59 ms to predict RAP > 8 mm Hg. Importantly, as described in Brechot et al.<sup>31</sup> we have confirmed that after excluding patients with elevated mean RAP, the correlation between IVRT and PASP was improved ( $r = 0.60$ ,  $P < 0.01$ ,  $n = 120$ ).

This is the first study to examine the usefulness of the IVRT in the estimation of PASP in a large PH population with a broad range of aetiologies.

In our study, IVRT, measured by DTI, was significantly higher in PH patients than in the group with normal PASP. As IVRT is heart rate dependent, it was divided by RR time interval (IVRT/RR%). The correlation of IVRT with RVSP and MPI was good but improved significantly when IVRT corrected for heart rate was

used. As a non-invasive method, IVRT was able to distinguish between patients with and without PH, regardless of the aetiology.

We identified that an IVRT cut-off of 75 ms provides high sensitivity and specificity for discriminating abnormally elevated pulmonary pressure.

Since DTI is widely available, the signal is relatively easy to obtain in almost all patients, more studies remain to be done with prospectively validating tissue Doppler techniques and its incorporation into clinical practice.

Study limitations

One of the limitations of this study is the presence of a heterogeneous population of patients who were not divided into groups with regard to aetiology.

We did not use angle correction to the measurement of IVRT by DTI. We do not believe that this is a major source of error, since we were measuring time intervals that are minimally affected by the angle of incidence.

The previously described<sup>33</sup> time delay (inertial interval) between the end of RV ejection and closure of tricuspid valve has not been considered, since phonocardiogram or haemodynamic recordings was not used in the study to evaluate this interval.

Moreover, we did not use ultrasound contrast agents or agitated saline to enhance technically inadequate TRV signals. This study was performed by an experienced sonographer (European certification) and we prefer to avoid the overestimation of Doppler velocities with the use of contrast secondary to contrast artefacts.

Lastly, due to the lack of data, we did not compare the estimated PASP by echocardiography with the right heart catheterization data, considered the gold standard. It might have provided more accurate information about the relationship observed between IVRT and PASP.

Conclusion

The determination of IVRT by DTI is a simple and reproducible method that correlates very well with RVSP. It is, therefore, a parameter to consider in the echocardiographic assessment of patients with PH, and may be particularly important when the tricuspid Doppler signal is poor.

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**Conflict of interest:** none declared.

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Ethical policy

The manuscript and the material within the manuscript have not been published and are not being considered for publication elsewhere in whole or in part in any language, including publicly accessible websites or e-print servers, except as an abstract.



The research study complies with the Declaration of Helsinki, and informed consent was obtained from the subjects. All authors have read and agree to the manuscript as written.

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