Usefulness of right ventricular isovolumic relaxation time in predicting systolic pulmonary artery pressure

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Aims Systolic pulmonary artery pressure (sPAP) cannot always be assessed from Doppler-detected tricuspid regurgitation (TR), especially when sPAP is normal. The right ventricular isovolumic relaxation time (rIVRT) is related to sPAP, and assessment of rIVRT by tissular Doppler imaging (rIVRT⁰) has recently been proposed as an alternative method for estimating sPAP in patients with pulmonary artery hypertension (PAH). We evaluated here its usefulness in everyday clinical practice.

Methods and results We conducted a prospective Doppler vs. catheterization study in 26 patients. TR was undetectable in 6 patients (32%) with normal sPAP and in one patient (14%) from those with PAH. rIVRT⁰ was recordable in all patients. We found a strong correlation between rIVRT⁰ and sPAP (r = 0.87; P < 0.0001). rIVRT⁰ had a high sensitivity in detecting PAH, and a rIVRT⁰ of 40 ms or less excluded PAH with a negative predictive value of 100%. We also found that a prolonged rIVRT⁰ is not specific to PAH and that the rIVRT⁰-estimated sPAP did not agree well with the catheter-evaluated value.

Conclusion Measurement of rIVRT⁰ can help estimate sPAP in the absence of TR: A normal rIVRT⁰ excludes PAH with a high negative predictive value. A prolonged rIVRT⁰ is in favour of an elevated sPAP but cannot affirm it by itself.

KEYWORDS
Doppler echocardiography; Right ventricular isovolumic relaxation time; Pulmonary artery pressure; Doppler tissular imaging; Cardiac catheterization; Prospective studies

Introduction

Non-invasive assessment of systolic pulmonary artery pressure (sPAP) is now a routine investigation in echocardiographic laboratories. The most common approach is to measure the peak velocity of a tricuspid regurgitant jet and apply the modified Bernoulli equation. However, the assessment of tricuspid regurgitation (TR) is thought to be problematic in ~20% of healthy subjects and up to 70% of patients suffering from chronic obstructive pulmonary disease (COPD). Contrast agents can be used to enhance the TR signal, but require venous catheterization. Other less invasive tools are required to estimate sPAP.

Forty years ago the right ventricular isovolumic relaxation time (rIVRT) was described as a tool to predict sPAP using phonocardiography. Although Hatle et al. characterized the parameter by Doppler ultrasonography its use remained technically demanding. Tissular Doppler imaging technique (TDI) rekindled interest in its use: In 2001, Caso et al. described rIVRT measured by TDI (rIVRT⁰) as a reliable tool for predicting pulmonary artery hypertension (PAH) in COPD patients. Further simultaneous Doppler-catheterization studies showed that rIVRT correlates well with sPAP. Recently, Dambrauskaite et al. described rIVRT as an efficient tool to predict sPAP in patients with PAH. The aim of the present study was to evaluate the feasibility and accuracy of rIVRT⁰ measurement for estimating sPAP in a population of unselected patients with a large range of sPAP levels.

Methods

This prospective study was conducted from November 2004 to May 2005 in the University Hospital of Bordeaux-Pessac, France. Every patient referred for routine right heart catheterization was eligible for the study. Exclusion criteria were: age <18 years, non-sinus rhythm, prosthetic tricuspid valve, haemodynamic instability (infusion of vasoactive drugs, depletion by diuretics at the time of the study), left ventricular hypertrophy (rIVRT⁰ was described to be increased in the absence of PAH during this condition), history of myocardial infarction (regional wall motion hypokinesis may impair TDI recordings). The cut-off value of 40 mmHg was chosen to define PAH because it seemed

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to us to be the most clinically relevant: In 2001, Mc Quillian studied a population of 15,000 healthy subjects. A sPAP >30 mmHg was found in 28% of individuals. All patients gave their written consent to participate in the study, which was approved by the local ethics committee.

Cardiac catheterization

Right heart catheterization was performed using a Swan-Ganz catheter (Edward Life Sciences sas ref 131F7) inserted through the right femoral vein after local anaesthesia. Pressure measurements were calibrated before the study from the midaxillary line. Right atrial pressure (RAP), right ventricular pressures, pulmonary systolic, diastolic, and occlusive pressures were determined. Triplicate measurements of thermodilution cardiac output were averaged. Cardiac index, arteriolar pulmonary resistance (APR), and total pulmonary resistance (TPR) were calculated.

The physician performing the cardiac catheterization was unaware of the results of Doppler examination and vice versa. Patients were at rest and did not receive sedatives.

Echocardiographic and Doppler studies

The echocardiographic study was performed the day before cardiac catheterization, with a mean interval of 12 h between the two measurements, in stable clinical status, and with unchanged therapy. Doppler echocardiography was performed with a General Electrics Vivid 7 Expert equipped with a M4S transducer. Patients underwent a routine transthoracic echocardiographic examination with standard measurements including sPAP estimation using TR. Non-invasive RAP was estimated from the dimensions of the inferior vena cava and its respiratory motion as described previously.16, 17 TDI measurements were conducted from the apical window at the lateral (right) corner of the tricuspid annulus, as described by Caso et al.11 This site has been shown to provide better correlation with sPAP than the apical segment of right ventricular (RV) free wall in Dambrauskaite’s study14 with comparable results as those from the basal segment. Sample size for pulsed TDI was 6 mm. rIVRT was measured as the time between the end of the systolic S’ wave (peak systolic tricuspid annular velocity) and the beginning of the diastolic E’ wave (Figure 1). Recordings were made at a sweep speed of 100 mm/s. An average of five cardiac cycles was recorded. As rIVRT is heart rate (HR)-dependent, adjusted rIVRT was calculated as rIVRT/√RR.

RV systolic function was assessed using S’ wave and RV systolic dysfunction was defined as a S’ <11.5 cm/s, as previously described.18 All Doppler echocardiographic and TDI recordings were obtained at end expiration.

Reproducibility

Ten echocardiographic and TDI recordings were performed with offline data analysis (Echopac, GE vingmed Ultrasound). These studies were conducted in a blinded manner by a second observer and by the first observer a second time. Measurements variability was expressed as mean ± SD of the difference between the two sets of observations, and the mean percentage error was calculated as the absolute difference between observations divided by the mean observation.

Statistical analysis

Continuous variables are reported as means ± SD. Paired t tests were used to assess differences in HR between cardiac catheterization and echocardiographic examination, and unpaired t tests for the subgroup analysis. Correlations between invasive sPAP, APR, TPR, and the Doppler parameters were established using linear regression and are expressed as correlation coefficients; Bland-Altman analysis19 was used to evaluate the agreement between invasive sPAP and TDI-estimated sPAP. Receiver-operating characteristics (ROC) curves were constructed for the rIVRT measurements for predicting sPAP of 40 mmHg or higher. Statistical significance was set at P < 0.05.

Results

Patient characteristics

This study included 26 consecutive patients, 16 males and 10 females. The mean age was 62 ± 14 years (20–83) and mean sPAP was 37 ± 20 mmHg (15–98). Referral diagnoses were valvular heart disease (n=10), idiopathic pulmonary hypertension (n=4), cardiomyopathy (n=4), systemic sclerosis (n=2), heart transplant (n=2), coronary artery disease (n=1), syncope (n=1), congenital heart disease (n=1), COPD (n=1). Seven patients had a sPAP >40 mmHg, 13 patients had a sPAP ranging from 25 to 40 mmHg, and 6 had a sPAP <25 mmHg. Individual as well as subgroup echocardiographic and haemodynamic variables are listed in Tables 1 and 2, respectively. There was no difference between HR during Doppler examination and during haemodynamic measurements. Only 3 patients had a right bundle branch block (RBBB), 2 with a normal sPAP, and one in the PAH group (Table 1).

Tricuspid regurgitation

An analysable Doppler tricuspid diastolic signal could not be obtained in 7 patients (27%). Six of them were in the group of patients without PAH, which means that TR was not recordable in 32% of patients in this group. All but one patient (86%) of the PAH group had an analysable tricuspid regurgitant jet. None of our patients had a more than trivial TR.

When feasible, the Doppler-estimated sPAP showed a strong correlation with the catheter-measured sPAP ($r = 0.94$, $P < 0.001$).

Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging

Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging and systolic pulmonary artery pressure

rIVRT was available in all patients. The mean rIVRT was 16 ± 10 ms in patients with sPAP <25 mmHg, 31 ± 23 ms in patients with sPAP between 25 and 40 mmHg, and 83 ± 34 ms in patients with sPAP >40 mmHg. rIVRT was significantly lower in the group without PAH than in the group with PAH (Table 2). Figure 2 shows the linear regression analysis between rIVRT and invasive sPAP. There was a strong correlation between rIVRT and invasive sPAP ($r = 0.87; P < 0.0001$). Correcting rIVRT for HR did not improve this correlation ($r = 0.83; P < 0.0001$). There was also a significant correlation between rIVRT and APR ($r = 0.84; P < 0.0001$), and between rIVRT and TPR ($r = 0.74; P < 0.0001$).

Figure 3 shows the Bland–Altman analysis of the agreement between TDI-estimated and catheter-measured sPAP. The mean differences between measured and estimated pressures were 0.02 ± 9.89 mmHg (range −18.14 to 19.02) in the whole population, −2.22 ± 7.89 mmHg in the no PAH group (range −17.79 to 10.66) and 0.55 ± 14.05 mmHg in the PAH group (range −18.14 to 19.02).
In the subgroup of patients with a rIVRT < 40 ms, the mean difference between the two was 1.21 ± 6.64 mmHg (–11.79 to 10.66). The ROC curve for predicting a sPAP of 40 mmHg or higher is shown in Figure 4. The area under the curve was 0.95 (95% confidence interval 0.88–1.03). In this study, a rIVRT > 59 ms predicted a PAH with a sensitivity of 86% and a specificity of 89.5%, and a rIVRT < 40 ms excluded it with a negative predictive value of 100%.

**Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging and right ventricular function**

S′ was significantly reduced in PAH patients (Table 2), and the rate of RV dysfunction was higher in this group (5/7 vs. 4/19 in the no PAH group; $P = 0.019$). rIVRT′ did not correlate well with S′ values ($r = 0.24; P < 0.0001$). Correlation between rIVRT′ and sPAP was reduced in patients with RV systolic dysfunction ($r = 0.79; P = 0.0098$) when compared with patients with a preserved RV systolic function ($r = 0.90; P < 0.0001$).

**Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging and right atrial pressure**

RAP was significantly higher in patients with PAH (Table 2), and we found a slight positive correlation between rIVRT′ and RAP in our population ($r = 0.39; P = 0.049$). Correlation between rIVRT′ and sPAP was also improved when patients with elevated RAP were excluded ($r = 0.89$;
A trend towards a reduced S’ wave in patients with elevated RAP was observed (11.6 ± 2.1 vs. 12.5 ± 1.1 cm/s in patients with normal RAP), but this did not reach statistical significance (P = 0.25). In contrast PAOP was significantly increased in patients with elevated RAP (16.8 ± 9.4 mmHg in this group vs. 10.3 ± 3.3 in patients with normal RAP; P = 0.01).

Table 1 Demographic and selected clinical, echocardiographic, and haemodynamic variables of individual patients (classified by rIVRT’ values)

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<th>dPAP, mmHg</th>
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<th>RAP, mmHg</th>
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S’, peak systolic tricuspid annular velocity; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; HR, heart rate; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; BMI, body mass index; F, female; M, male; DCM, dilated cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; CHD, congenital heart disease; CAD, coronary artery disease; HT, heart transplant; AR, aortic regurgitation; Sscl, systemic sclerosis; AS, aortic stenosis; PPH, primitive pulmonary hypertension.

Table 2 Mean and range of echocardiographic and haemodynamic characteristics of the patients

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<th>PAH group (sPAP &gt;40 mmHg)</th>
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F, female; M, male; S’, peak systolic tricuspid annular velocity; CI, cardiac index; APR, arteriolar pulmonary resistance; TPR, total pulmonary resistance. *P < 0.05; **P < 0.01; ***P < 0.001.
When patients with RV systolic dysfunction and elevated RAP were excluded, correlation between rIVRT and sPAP reached $r = 0.94 \ (P < 0.0001)$ in the 12 patients left.

**Reproducibility**

Measurements on recorded loops provided an intra-observer variability of $1.4 \pm 7.8 \ \text{mmHg (15 \pm 15\%, \ P = 0.53)}$ and an inter-observer variability of $2.0 \pm 8.9 \ \text{mmHg (14.5 \pm 21.4\%, \ P = 0.51)}$.

**Discussion**

In this Doppler-catheterization study, we found a strong correlation between right ventricular isovolumic relaxation time measured by TDI (rIVRT) and sPAP. This result is consistent with numerous studies conducted from 1967 to 2006. Such a correlation raises the question of evaluating sPAP using rIVRT.

![Figure 2](https://academic.oup.com/ehjcimaging/article-abstract/9/4/547/2403095)

**Figure 2** Linear regression analysis between rIVRT and invasive sPAP ($r = 0.87; \ P < 0.0001$). *, two points overlapped.

**Usefulness of rIVRT in systolic pulmonary artery pressure**

Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging is a reliable tool for excluding PAH in normal subjects. In particular, we found that a rIVRT < 40 ms predicted a normal sPAP with a negative predictive value of 100%. This is in agreement with other studies, in which none of the patients with a rIVRT < 40 ms had PAH, as long as HR remained < 115 bpm. This is of particular interest because the proportion of patients with non-recordable TR increases with decreasing pulmonary artery pressure (rising from ~5% in patients with PAH to ~20% in healthy subjects in the most recent studies), which makes it difficult to affirm the normality of sPAP in healthy subjects. In contrast, rIVRT assessed by TDI was obtained in at least 96% of the patients in previous studies. In our study, TR was recorded in 70% of patients with normal sPAP and in 86% of patients with PAH, whereas rIVRT was recorded in all patients. rIVRT affirmed a normal sPAP in five out of the seven patients without recordable TR.

**Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging measurement is less efficient as a continuous marker of systolic pulmonary artery pressure**

(i) A prolonged rIVRT is not specific to PAH: It has been reported to be prolonged in patients with hypertrophic cardiomyopathy, right ventricular dysfunction, or right bundle branch block. On the contrary, it was shown to be pseudo-normalized in patients with elevated RAP or tricuspid insufficiency. This may limit its use in patients with PAH, who are more likely to exhibit these
(ii) Despite a strong correlation between rIVRT-predicted sPAP and invasive sPAP, two standard deviations in our Bland–Altman analysis represent discrepancies between the two methods of up to 20 mmHg. (iii) Inter- and intra-observer variability was quite high,

In respect to these limitations, a prolonged rIVRT may indicate an elevated sPAP in combination with other parameters, such as pulmonary flow acceleration time or pulmonary regurgitant flow velocity. We found in our population that a rIVRT of 59 ms predicted a sPAP of 40 mmHg or higher with a sensitivity of 86% and a specificity of 89.5%. Furthermore, correlation between rIVRT and sPAP was improved when patients with RV dysfunction and elevated RAP were excluded. This finding should be investigated on a large effective.

**Right ventricular isovolumic relaxation time pathophysiology**

rIVRT duration is determined by: (i) The difference between sPAP and RAP: The interval required for RV pressure to decrease from the pulmonary valve closure pressure to the tricuspid valve opening level increases with increasing sPAP. (ii) Right ventricular diastolic function: RV dysfunction decreases the rate of fall of right ventricular pressures during relaxation, thus increasing rIVRT. This mechanism was in particular well described during hypertrophic cardiomyopathy. (iii) HR, inversely related to rIVRT. Other mechanisms have been proposed: Shaver et al. described a ‘hanged-out’ interval of 30 to 80 ms between the end of right ventricular systole and the pulmonary valve closure. The interval decreased with increasing dPAP, thus lengthening rIVRT. In an animal study, Myhre et al. described pulmonary artery impedance as being the principal determinant of rIVRT, as neither RAP nor HR were correlated with rIVRT.

Considering the pathophysiology of rIVRT, it appears clearly that HR, RV dysfunction and RAP may perturb the evaluation of sPAP with rIVRT.

**Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging and heart rate**

Correlation between rIVRT and sPAP was not improved by correcting rIVRT for HR, as described by others. This is probably because HRs were in the same range in our population, and corrected rIVRT may be useful in case of extreme HR.

**Right ventricular isovolumic relaxation time measured by Tissular Doppler imaging and right ventricular function**

In this work we used S’ wave to assess RV function. The rate of RV dysfunction was significantly higher in patients with PAH, as described previously. Interestingly, correlation between rIVRT and sPAP was poorer in patients exhibiting RV dysfunction. This result is consistent with data published by Dambrauskaite et al. in PAH patients, showing that correlation between rIVRT and sPAP was reduced in patients having a tricuspid annular plane systolic excursion <18 mm. rIVRT was also described to be prolonged during RV dysfunction in the absence of PAH.

According to the above physiologic principles, an increase in RAP should shorten rIVRT. Abbas et al. in a Doppler-catheterization study in 21 patients noted an inverse relation between RAP and rIVRT, as expected. Yoshifuku et al. also described rIVRT’ to be pseudo-normalized in

![ROC Curve](image-url)
patients with elevated RAP during acute right ventricular myocardial infarction. In our study, RAP was higher in patients with PAH and we found a slight positive correlation between RAP and rIVRT. This is probably because the increase in RAP was a consequence of elevated left ventricular filling pressures and hypervolemia in our population, as opposed to Abbas’ and Yoshifuku’s patients where the principle mechanism was RV failure. Indeed we found only a trend towards a reduction of S’ wave in patients with elevated RAP in our study, whereas they exhibited a PAOP significantly higher.

Correlation between rIVRT and sPAP was further improved when patients with elevated RAP were excluded. We therefore believe that elevated RAP may also influence the evaluation of sPAP with rIVRT.

Study limitations

In our study, rIVRT-measured sPAP was compared with a reference method in a population of unselected patients exhibiting a large range of sPAP. We focused on the clinical usefulness of this parameter. To our knowledge it is the first time that rIVRT was studied in patients with both normal and elevated sPAPs. This allowed to validate it as a good tool for identifying patients not having PAH, to highlight its limits as a continuous marker of sPAP and to detect the presence of false positive patients for this parameter. However, our study suffers from limitations: although our results were consistent with previous studies and reached statistical significance, our population was small, and in particular contained only 7 patients with PAH. Therefore conclusions on PAH patients are of limited value, as well as ROC curve, and the cut-off limit for normal and abnormal values of rIVRT should be further confirmed in a larger effective.

Only one patient suffering from COPD was included in this study. TR assessment is particularly difficult in such patients, and rIVRT may be of particular interest for assessing sPAP in these patients. Our cohort also contained only 3 patients with RBBB, so that we could not analyse the influence of RBBB on the evaluation of sPAP with rIVRT. The Doppler examination and invasive measurements were performed within 12 h of each other, but patients were haemodynamically stable and the correlation between the two techniques remained close. As we focused on haemodynamically stable patients, it is unclear whether our conclusions would remain true in case of acute PAH, such as pulmonary embolism.

Conclusions

rIVRT appears to be helpful in evaluating sPAP: a normal rIVRT (<40 ms) can exclude PAH with a high negative predictive value. A prolonged rIVRT is indicative of PAH but cannot affirm it by itself.

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