The Age of Non-Invasive Measurements: Echocardiographic Equations Methods to Determine Variables in the Pulmonary Vascular Reactivity Test

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Introduction

Pulmonary vascular resistance is a hemodynamic variable very useful for the management of patients with advanced pathologies cardiovascular and pulmonary, to evaluate the therapeutic response in patients with congestive heart failure [1,2]. Evaluation of patients candidates for cardiac and liver transplant [3-7], is a prognostic parameter for patients with congenital diseases [8], is considered a critical parameter for evaluating PH independent of etiology [9]. The PVR is calculated invasively by the relation of the pressure gradient and the flow transpulmonary [10], Abbas and collaborators [11,12] proposed to estimate the measurement echocardiographic of the PVR by the relation TRV/TVI representing the method most used currently, among others proposed for its calculation [13-18]. On the other hand, the PVRT has very precise indications according to the European Society Cardiology guidelines [9] for the diagnosis, treatment and prognosis of the PH. Right catheterization is considered as the gold standard for the definitive diagnosis of PAH and the method of choice for PVRT [19]. There aren’t reports of studies comparing in the PVRT simultaneous measurements of PVR and MPAP with the invasive method and the Echocardiography Doppler. In this investigation we raised 3 objectives: 1) Revalidate Abbas’s equation in a group of patients [20] with indication of Right Heart Catheterization (RHC) diagnosis. 2) Compare the invasive and non-invasive measurements of MPAP and PVR in a group of patients who underwent the PVRT and verify the effectiveness of the echocardiographic measurements. 3) Demonstrate in this group of patients the utility and efficiency of a novel Echocardiographic equation to calculate the PVR when compared with the Abbas’s equation [10] and the RHC.
Methods

Population and sample

It's a prospective, double-blind, observational study that was divided into two stages, the first part was selected 20 patients, 10 patients with admission to Intensive Care Unit (ICU) and placement of Swan Ganz catheter for presenting medical pathologies that merited measurement of hemodynamic variables; 10 patients in the Center's cardiology department consultation or hospitalization, with indication of right catheterization to confirm diagnosis clinical and echocardiographic of PH. No distinction was made for age group, sex, comorbidity, or medication was omitted (Table 1). All patients entered our center in the period from February to August 2008.

Exclusion criterion

Regurgitation tricuspid >2+. The clinical, hemodynamic and demographic characteristics are shown in table 1.

In the second part of the study were included 11 patients referred to the medical consultation, of pneumonology, pediatric cardiology and adult cardiology of the same center with presumptive diagnosis of PH, of different etiology, degree of severity and echocardiographic criteria for Perform the pulmonary vascular reactivity test. These patients were studied from July to December 2009 (Table 2).

Exclusion criterion: Patients with hemodynamic instability, chronic or acute hypoxemia, coagulation disorders.

One patient was removed from the study because of the inability to perform measurements with the catheter and in 2 patients only one measurement was made. All patients in the Department of Cardiology (both stages) signed informed consent. Table 3 shows the values obtained in the 10 patients of the PVRT of the TRV/TVI index, the first Abbas equation, applying the Abbas algorithm and RHC. Table 4 shows the values obtained from MPAP calculated with the Chemla equation and RHC at times 0 (t0), 30 minutes, (t30) and recovery (tR) of the test.

Table 1: Clinical, hemodynamic and demographic characteristics of patients (group 1).

<table>
<thead>
<tr>
<th>SEX (M/F)</th>
<th>AGE (range)</th>
<th>Ejection fraction (range)</th>
<th>MPAP (range)</th>
<th>Pulmonary capillary pressure</th>
<th>Mean (range)</th>
<th>Ejection fraction (range)</th>
<th>MPAP (range)</th>
</tr>
</thead>
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<tr>
<td>15/5</td>
<td>48 (21-78)</td>
<td>55 (30-75)</td>
<td>20 (13-30)</td>
<td>12 (6-20)</td>
<td>12 (12.2-2.02)</td>
<td>1.7 (1.28-2.95)</td>
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Table 2: Clinical, hemodynamic and demographic characteristics of patients (group 2).

<table>
<thead>
<tr>
<th>SEX (M/F)</th>
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<th>Ejection fraction (range)</th>
<th>MPAP (range)</th>
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<th>Mean (range)</th>
<th>Ejection fraction (range)</th>
<th>MPAP (range)</th>
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<td>5/5</td>
<td>47 (27-63)</td>
<td>55 (30-75)</td>
<td>27 (17-62)</td>
<td>12 (8-31)</td>
<td>8</td>
<td>0</td>
<td>2</td>
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Table 3: Invasive and non-invasive measurements of Pulmonary Vascular Resistance in the pulmonary vascular reactivity test.

<table>
<thead>
<tr>
<th>TRV/TVI</th>
<th>PVR (eco)</th>
<th>PVR (algorithm)</th>
<th>PVR (cat)</th>
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<tbody>
<tr>
<td>0.14</td>
<td>1.56</td>
<td>1.56</td>
<td>1.25</td>
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<tr>
<td>0.16</td>
<td>1.76</td>
<td>1.76</td>
<td>1.8</td>
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<tr>
<td>0.22</td>
<td>2.36</td>
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<td>2.16</td>
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<td>0.23</td>
<td>2.46</td>
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<td>3.8</td>
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<tr>
<td>0.24</td>
<td>2.56</td>
<td>2.56</td>
<td>4.18</td>
</tr>
<tr>
<td>0.25</td>
<td>2.66</td>
<td>2.66</td>
<td>4.2</td>
</tr>
<tr>
<td>0.36</td>
<td>3.76</td>
<td>8.9</td>
<td>11.5</td>
</tr>
<tr>
<td>0.38</td>
<td>3.96</td>
<td>7.36</td>
<td>16.4</td>
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<tr>
<td>0.53</td>
<td>5.46</td>
<td>10</td>
<td>10.5</td>
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<tr>
<td>0.8</td>
<td>8.16</td>
<td>13.33</td>
<td>14.37</td>
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</table>

*Obtained from the Abbas equation PVRcat=10×TRV/TVI*0.16.

The study was approved by the Bioethics and Medical Ethics Committee of the medical institution.

Echocardiography

The Doppler and two-dimensional measurements were performed with the Philips Sonos 7500 S3 and Philips IE33 SE1 equipment According to American Society Cardiology guidelines [20]. The TRV/TVI* index was determined by Doppler echocardiography using the view of the short parasternal axis at the level of large vessels. The TVI* (cm) was obtained with pulsed Doppler by...
Table 4: Invasive and non-invasive measurements of MPAP during stages t0, t3 and recovery (R) from PVRT.

<table>
<thead>
<tr>
<th>MPAP t0</th>
<th>MPAP Ct t0</th>
<th>MPAP t30</th>
<th>MPAP R</th>
<th>MPAP Ct R</th>
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<td>50</td>
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<td>50</td>
<td>51</td>
<td>63</td>
</tr>
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</table>

*MPAP = 0.61 × SPAP + 1.95.

The images were reassessed to quantify the reliability of the intraobserver and interobserver. The Intraclass Correlation Coefficient (ICC) was determined for variability inter and intraobservers; the relationship between the force of agreement and ICC were analyzed. The Kappa coefficient was also estimated to assess the degree of interobserver concordance.

Results

The first group found analyzed a PCP greater than 12 mmHg was found in 7 patients. 10 patients presented left heart disease of different etiology (Table 1). The linear correlation analysis between PVR ct and TRV/TVI rvot showed high correlation (R²=0.95, 95% CI). The equation derived from linear regression was PVR ct = 10 × TRV/TVI rvot + 0.36 (Figure 1).

Applying the analysis of Bland-Altman, the values of PVR of this equation showed satisfactory limits in accordance with the PVR ct with average value 0.36 (SD: 0.13-0.6) (Figure 2).

In the second group analyzed (Table 2), 8 of them presented PCP equal or less than 12 mmHg, being varied the subgroups within the classification of PH accepted by ESC: 1.4.4. Congenital heart disease: interatrial communication [2], Interventricular communication [1], 2.3. Valvular: Mitral valvulopathy type severe insufficiency [2], Aortic and mitral valvulopathy type double lesion, both mild [1], 3.1. Severe COPD+Severe PH [3] and 3.5 Diseases of pulmonary development: Dilation of the pulmonary artery trunk [1]; unlike the first group, most patients reported high PVR values for being candidate patients of the PVRT (Table 2).

In the second stage of the study, the analysis of linear correlation between PVR ct and TRV/TVI rvot basal showed good correlation (R²=0.70, 95% CI) that was exceeded by excluding the highest values of PVR ct (R²=0.92, 95% CI) (Figures 3 and 4).
Figure 1: Linear regression analysis between PVR by right catheterization and the ratio TRV/TVI_{RVOT} obtained by Doppler echocardiography.

Figure 2: Analysis of Bland-Almant showing the limits of agreement between PVR_{CATH} and PVR_{ECHO}.

There was also a report of high correlation between the two methods by excluding the 3 highest values at 30 minutes of the test and in the recovery stage ($R^2=0.89$ in both cases) (Figures 5 and 6). Prior to exclusion, the correlation coefficient was $R^2=0.56$ with the first equation of Abbas and $R^2=0.64$ when applying its algorithm (Figure 7).

The Youden's index was estimated obtaining a cut value in the ratio TRV/TVI_{RVOT} of 0.24 provides 95% sensitivity and 100% of specificity to determine PVR_{CATH} of 4.67 WU in the basal stage of the PVRT (Figure 8). Receiver Operating Characteristic (ROC) curve. In addition to the above, it shows AUC of 1.95% confidence interval between 0.692-1 and significance nivel p<0.0001 (Figure 9).

We found very high correlation ($R^2=0.97$) when comparing values obtained from PVR by the Abbas algorithm (if TRV/TVI_{RVOT}<0.275 index, $PVR_{ABBAS}=TRV_{RVOT}/TVI_{RVOT} \times 5$ and the equation proposed in this work: $PVR=(TRV \times RVD/TVI_{RVOT}) \times Cardiac output correction factor (cfCO TVI_{RVOT})$ (Figure 10). The correlation obtained when both equations were compared with the values of RHC were high ($R^2=0.78$ and $R^2=0.84$, respectively) (Figures 11 and 12) Bland Altman's analysis showed satisfactory agreement limits between the methods with average differences similar between the methods (Figures 11 and 12).

We obtained MPAP values by echocardiography from the formula proposed by Chemla D, et al. [23]: $PMAP=0.61 \times PSAP+1.95$. High correlation was found in the linear regression analysis between MPAP_{echo} and MPAP_{cath} during times baseline, 30 minutes and recovery (0, 130 and 18) ($R^2=0.87, 0.89, 0.99$) (I.C. 95%) (Figure 13). Bland Altman's analysis showed satisfactory concordance limits in all
Figure 6: Linear regression analysis between the invasive PVR and the ratio $\frac{TRV}{TVI_{RVOT}}$ obtained in the recovery stage of the PVRT and after excluding the 3 highest values.

Figure 7: Linear regression analysis between $PVR_{CATH}$ and the VRT/ITV$_{RVOT}$ relationship obtained in step t30 of the PVRT when applying the Abbas algorithm.

Figure 8: Cut-off value 0.24 gave 95% sensitivity and 100% specificity to determine RVP$_{CATH}>4.67$ WU in the basal stage of PVRT.

Figure 9: Receiver Operating Characteristic (ROC) curve. A $\frac{TRV}{TVI_{RVOT}}$ ratio of 0.24 (blue) and provided the best-balanced sensitivity and specificity to determine patients with PVR>4.67 WU (areas under the curve [AUC]) of 1.

Figure 10: Linear regression analysis and Bland Altman between the PVR obtained by the Abbas algorithm and the equation proposed in this study (PVRt).
cases, with average differences between the RHC of: 2, -0.75 and -1 (Figure 14). The TRVP reported negative in all patients. The CCI was 0.78 between observers and 0.90 observers with excellent agreement force. The Kappa coefficient inter observer was 0.83 with an almost perfect concordance force.

Discussion

15 years have passed since Abbas AE, et al. [11] published a simple Doppler echocardiographic equation: \( PVR = 0.16 + \frac{TRV}{TVI_{rvot}} \times 10 \). As we know, the PVR is directly related to the Pressure Gradient (\( \Delta P \)) and inversely with cardiac output (CO), according to this author; its equivalents echocardiographic would be represented by the TRV as a measure of pressure gradient and TVI as a Cardiac flow measurement. Unfortunately the work presented had a great limitation because it excluded all patients with moderate and severe tricuspid regurgitation representing the population that could be most favored. In successive years, emerged publications aimed at giving validity to this equation [32-36], discuss its content 16-18 or establishing different approaches and hemodynamic variables for the calculation of PVR [13-16,37,38].

One of the works proposed by another variable echocardiographic to determine the PVR is that presented by Gurudevan SV, et al. [14], they concluded that there is an inverse correlation between systolic velocity of Tricuspid Annulus (\( tSm \)) and PVR, determining that a velocity <10 cm/s equals a PVR >12.5 UW. Haddad F, et al. [13] proposed an index to obtain PVR\_echo = SPAP/(HR × TVI\_rvot) where a cut value of 0.076 provided 86% sensitivity and 82% specificity to determine IPVR>15 WU/m^2. He also mentioned that patients with elevated values of PVR didn’t correlated well using the equation proposed by Abbas (\( R^2=0.46 \)), but with the lowest values yes.

An index proposed by Scapellato F, et al. [15], requires the measurement of the Pulmonary Pre-ejection Period (PPEP), Pulmonary Acceleration Time (PAT) and Total Systolic Time (TST) (PVR=PPEP/PAT/TST; reported high correlation with PVR obtained by catheterization Cardiac(\( R^2=0.96 \)). An index>2.6 predicts a PVR>2.5 WU when the resistances are between 0-8 WU. This equation didn’t apply in the work of Haddad F, et al. [13] by low correlation (\( R^2=0.30 \)).

Vlahos AP, et al. [32] conducted a prospective study in 12 patient’s candidates for liver transplantation and obtaining PVR by right catheterization. They analyzed the index TRV\_TVI\_rvot and TRV/TVI\_rvot corrected by the diameter of the RVOT, finding that both correlated well with PVR\_cath (\( R^2=0.711 \) and \( R^2=0.731 \), respectively), even in patients with elevated values of PVR. They concluded in their study that the relationship TRV\_TVI\_rvot with a value of 0.38 can provide a specificity of 100% for PVR of 8 WU.

Opotowsky AR, et al. [17], in 2013 published a paper where they derive 2 equations to estimate the PVR from the relationship between SPAP and TVI\_rvot, validated these equations and compared with the equation of Abbas AE, et al. [11] (model 1). The derived models were: PVR=1.2 × SPAP/TVI\_rvot (Model 2) and PVR=(SPAP/TVI\_rvot)+3, if the systolic notch is present (Model 3). They found that model 1 consistently underestimated the PVR estimated by catheterization, especially for those with high PVR. The derivative models showed no bias, model 3 was best correlated with PVR\_cath (\( R^2=0.80 \) vs \( R^2=0.73 \) and \( R^2=0.77 \) for Models 1 and 2, respectively). This approach caused discomfort in Abbas AE, et al. [11], because precisely in that year, they published an article 12 proposing a new equation: PVR\_echo = TRV^2/TVI\_rvot × 5-0.4.
for patients with higher PVR who had a TRV/TVI \textsubscript{rvot} index ≥ 0.275, being this cut-off point for PVR>6 UW (ROC curve). Currently his two works have worldwide acceptance and recognition and PVR\textsubscript{echo} equation=RTV/TVI \textsubscript{rvot} × 10+0.16, is part of the list of hemodynamic variables validated and obtained by Doppler echocardiogram.

In a more current work (2017), Kaga S, et al. [16], proposed an equation based on the difference of the initial and final diastolic pressure gradient obtained by means of Pulmonary Regurgitation (PR) and CO: (early-diastolic PA-RV pressure gradient-end-diastolic PA-RV pressure gradient)/echocardiographic cardiac output. They analyzed the linear correlation between the Abbas equations (2003 and 2013) and the Scapellato equation with catheterization, obtaining correlation coefficients of 0.54, 0.66 and 0.54 respectively. The best correlation with catheterization was obtained for the equation proposed in its work (R\textsuperscript{2}=0.81) followed by the index of Lindqvist (0.76) [39].

In the present work, with the first group of 20 patients, validated the usefulness of this equation, presenting a small discrepancy in the value of the correlation constant: PVR\textsubscript{echo}=TRV/TVI \textsubscript{rvot} × 10+0.16, is part of the list of hemodynamic variables validated and obtained by Doppler echocardiogram.

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MPAP was obtained by means of the equation proposed by Chemla D, et al. [23]: MPAP = 0.61 x SPAP + 1.95 and the PVR with the relationship TRV/TVI to evaluate its behavior in high values of PVR.

Two relevant findings were evidenced with the calculations: 1. The measurements of MPAP obtained by this formula were sustained similar to those reported by the catheterization in all phases of measurement of the test (t0, T30 and TR) with high linear correlation (R²=0.87, 0.99 and 0.98, respectively). 2. The correlation coefficient obtained when comparing the PVR_cho and PVR_reth values ascended from R²=0.70 to R²=0.78 when we applied the Abbas algorithm and in the cases with VRT/TVI ≤ 0.275 it increased even more when omitting the highest values, R²=0.92 (t0), R²=0.89 (t30 and tR). The cut-off point (TRV/TVI ≥ 0.275) specifies when in the linear regression analysis the correlation ceases to be linear to define the relationship between variables by an exponential growth curve, expressing the basis of the Abbas algorithm in its second work.

It's evident analyzes these finding that the TVI index, variable of the TRV/TVI index, is responsible for widening the gap between invasive and non-invasive methods. Very possibly by not taking into account the dilation of the right ventricle present in all cases of patients with elevation PVR [40,41]. It’s thus this work proposes an equation with reasoning more pathophysiologic than statistical, incorporating in its calculation. We also include a correction factor of the CO applicable in all patients according to the value of TVI that we call cCOTVI suggested by the repeated observation of its decrease proportional to the degree of dilatation and systolic dysfunction of the RV. This corresponds approximately to the near value of the CO if we divide the TVI between 2 when its value is below 10 cm, above this value, we will find normal values of CO (4-6 L/min) allowing to standardize it to 5. At the other end, TVI values below 6 would correspond to a very low CO estimate with probable severe right heart failure or shock (heart rate (CI) <2.2 L/min/m²).

The proposed equation is as follows:

$$PVR_{echo} = \left(\frac{TRV \times RVD}{TVI}\right) \times cfCOTVI_{TIVO}$$

$$TVI_{RVO} \leq 10 \times cfCOTVI_{RVO} = TVI_{RVO} \div 2$$

if $$TVI_{RVO} \geq 10 \times cfCOTVI_{RVO} = 5$$

The linear regression analysis between the values obtained from PVR with this equation and that of Abbas with his algorithm reported a high correlation, R²=0.97, when comparing the algorithms of Abbas, the PVR with the RHC, we obtained a greater correlation with our proposal (R²=0.84).

Limitations: low number of patients to perform the TRVP, however it is important to note that a total of 50 measurements were made. In all cases where it is not possible to measure the TRV or TVI, it will not be possible to perform the PVR calculations, not representing the case of this investigation.

Conclusions

In this work we conclude: 1. The algorithm of equations proposed by Abbas to determine PVR according to the relationship TRV/TVI is ≥ 0.275 is useful and easy to estimate [2]. The equation proposed in this work: $$PVR_{echo} = \left(\frac{TRV \times RVD}{TVI}\right) \times cfCOTVI_{TIVO}$$ is practical and applicable in all cases of pulmonary hypertension, representing an alternative to that offered by Abbas AE, et al. [13]. It's possible to perform the PVR, TRVP through of Doppler echocardiography based on the high correlation found in this work between the values of MPAP and PVR when compared with the invasive method and echocardiographic.

Recommendations

Further studies of TRVP are recommended by comparing both methods (echocardiography, RHC) to give more statistical weight and validity to echocardiographic methods and therefore, the applicability in the test.

Conflicts of Interest

The authors of the present work do not declare conflicts of interest.

Acknowledgement

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References


