Sensitivity of the Doppler Rate of Pressure Rise to Changes in the Inotropic State: an Experimental Comparison with Invasively Obtained dP/dt

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Aims: To investigate the sensitivity of the rate of pressure rise obtained by Doppler to changes in the inotropic state by comparing it to simultaneous invasive measurements of dP/dt under different conditions of contractility.

Methods and Results: Mitral regurgitation was provoked in five pigs, and simultaneous measurements of dP/dt and the Doppler-estimated rate of pressure rise were made with a micro-manometer and with continuous-wave Doppler. Changes in the inotropic state were induced by drug infusion and by ischaemia. One hundred and twenty-seven simultaneous measurements were made with a correlation coefficient between the Doppler-estimated rate of pressure rise and dP/dt of 0.85 (P<0.001). Sensitivity to inotropic changes was estimated as the percentage change of each parameter in each condition of contractility, and showed that the Doppler-estimated rate of pressure rise had better sensitivity than dP/dt.

Conclusion: The sensitivity of Doppler-estimated rate of pressure rise to changes in the inotropic state is greater than that of dP/dt. The correlation between the rate of pressure rise obtained by Doppler and dP/dt is maintained even in extreme conditions of contractility. Therefore, the rate of pressure rise can be considered a good parameter to assess linear changes of contractility.


Key Words: Doppler echocardiography; ventricular performance; mitral regurgitation, dP/dt.

Introduction

The maximum value of the first derivative of left intraventricular pressure curve (dP/dt) is a parameter of ventricular performance with high sensitivity to changes in the inotropic state[1,2]. dP/dt can be assessed non-invasively in patients with mitral regurgitation, since the intraventricular pressure curve can be constructed from the curve of regurgitant flow, recorded using continuous-wave Doppler, by application of Bernoulli’s simplified equation[3]. This Doppler-derived ventricular pressure curve correlates well with curves obtained using a micro-manometer, and the values of the first derivative of both curves are also well correlated[4]. In order to avoid the complex process of obtaining the first derivative of the Doppler-derived left intraventricular curves, Bargiggia et al[5] developed a simple method to obtain the rate of increase in left ventricular pressure that causes the mitral regurgitant flow to accelerate from 1 to 3 m/s. This value was called the rate of pressure rise (RPR), and represents the mean value of the pressure rise in a definite interval, thus underestimating the real value of dP/dt, which is the maximal increase in pressure. Despite this, RPR correlates well with invasive values of dP/dt[4,5] and with other more frequently used parameters of left ventricular function[6]. To our knowledge, the main virtue of dP/dt — its sensitivity to changes of contractility — has neither been studied for RPR nor compared with that of dP/dt, the invasive value of reference. The purpose of this study was to analyse the sensitivity of RPR to changes in the inotropic state by comparing the changes in the value of RPR against the simultaneous invasive measurements of dP/dt, and studying the correlation between them in extreme conditions of contractility.

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Methods

Animal Preparation

Five pigs weighing between 40 and 70 kg were used. Each one had previously been pre-medicated with fentanyl (2 µg/kg). General anaesthesia was induced with α-chloralose (50 mg/kg iv). They were mechanically ventilated and submitted to muscle relaxation with succinylcholine. Intravenous infusion of α-chloralose was continued (30 mg/kg/h) until the end of the experiment. All manipulation of animals was carried out in accordance with regulations set down by the European Union and conformed to the Position of the American Heart Association on Research Animal Use. The femoral artery was dissected, and a Millar 8F micro-manometer-tipped catheter (Millar Instruments, U.S.A.) was introduced, placed in the left ventricle. Median sternotomy and pericardiotomy were performed. A 5F catheter was introduced by direct puncture into the left atrium, and atrial pressure was recorded continuously with a membrane transducer. The anterior inter-ventricular artery was isolated by blunt dissection and a silk loop was passed underneath it.

Induction of Mitral Regurgitation

An 8F introducer was placed by Seldinger’s technique into the left ventricle, through the free ventricular wall between the atrioventricular sulcus and the first diagonal artery. The intraventricular placement of the introducer was guided by epicardial sonogram in order to place the tip between chordae tendinae. Movement of the introducer caused distortion of the subvalvular apparatus. This method allowed us to induce mitral regurgitation at various degrees and in various directions at will. Colour-coded epicardial echocardiography showed the direction of the jet and its magnitude, both to permit a good alignment of the continuous-wave Doppler and to avoid severe regurgitation, which could cause haemodynamical instability.

Measurement of RPR

A Toshiba sonos SSH 140 A echocardiograph (Toshiba Inc., Japan) was used for echographic recording with a 3·5 MHz transducer, which allowed measurements of time in Doppler recordings with an error of ±2 ms. Doppler scanning was performed from the epicardium, and the ultrasound beam was aligned with the help of colour-coded Doppler. The Doppler curve and the dP/dt values were recorded simultaneously, with analysis of RPR by application of Bargiggia’s formula, \( RPR = 32/\Delta t \), where 32 is the difference in pressure that generates an acceleration of the regurgitant jet from 1 to 3 m/s, and \( \Delta t \) is the time necessary for this change in mm of mercury per second. All the measurements were recorded on videotape. The variability of the measurement of RPR was tested retrospectively in 30 randomly-selected videotape images. Signals were processed twice by the same observer, 2 weeks apart, in order to determine intraobserver variability and by a second observer to determine interobserver variability.

Measurement of dP/dt

The micro-manometer tipped catheter was connected to an amplifier, then carefully calibrated before being introduced in the artery and heart. A differentiator was connected to the amplifier. Curves of dP/dt were recorded in paper, with printed time marks each 5 s.

Induction of Changes in the Inotropic State

Contractility was modified by induction of ischaemia and by intravenous infusion of drugs. The following protocol was used:

1. At least three basal measurements were done.
2. Diltiazem was used in intravenous boluses at 0·35 mg/kg and 0·70 mg/kg doses. Measurements were done for and after 5 min.
3. Dobutamine was infused intravenously at increasing doses from 10 to 40 µg/kg, for 5 min each. Measurements were done during and after that period of time.
4. Ischaemia was induced by tightening the silk loop previously passed around the left anterior inter-ventricular artery for 5 min. Measurements were done for and after 5 min.

Ten minutes were allowed between each manoeuvre to let the heart recover from the previous condition. The duration and number of measurements of each part of the protocol depended on the tolerance of the animal. With the fourth animal dobutamine was not used because it caused a severe intraventricular gradient and a pressure fall. The rest of the manoeuvres and measurements were performed, and are shown in Table 1.

Statistical Analysis

Statistical analysis was performed with the statistical package SPSS® 6.0 for Windows®. Linear regression analysis was used for the study of the correlation between RPR and dP/dt. Multiple regression analysis was used to assess the influences of mean atrial pressure and dP/dt on the values of RPR. The sensitivities of both RPR and dP/dt to changes in the inotropic state were determined by a previously described method as the average percentage change for each condition relative to...
Table 1. Comparison between the relative sensitivity of RPR (rate of pressure rise by Doppler) and dP/dt to inotropic changes in different conditions of contractility.

<table>
<thead>
<tr>
<th>Pig</th>
<th>No meas/condition</th>
<th>dP/dt mmHg/s</th>
<th>RPR mmHg/s</th>
<th>LVP mmHg</th>
<th>ΔdP/dt</th>
<th>ΔRPR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 Dobutamine</td>
<td>1596 ± 0</td>
<td>1334 ± 0</td>
<td>113 ± 4</td>
<td>12 ± 8</td>
<td>25 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Basal</td>
<td>1788 ± 129</td>
<td>1673 ± 162</td>
<td>124 ± 6</td>
<td>12 ± 8</td>
<td>25 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>Dobutamine</td>
<td>1524 ± 16</td>
<td>1295 ± 269</td>
<td>90 ± 5</td>
<td>4 ± 5</td>
<td>3 ± 19</td>
<td>0.27</td>
</tr>
<tr>
<td>8</td>
<td>LAD clamp</td>
<td>1541 ± 137</td>
<td>1119 ± 385</td>
<td>85 ± 7</td>
<td>−3 ± 8</td>
<td>−16 ± 29</td>
<td>0.067</td>
</tr>
</tbody>
</table>

The results of the comparison between the relative sensitivities of RPR and dP/dt in each condition and in each pig were compared by the Wilcoxon test for non-parametric paired samples. The SYX comparison was used to test the differences between the slopes of the regression curves. A value of P of less than 0.05 was considered statistically significant.

**Results**

One hundred and twenty-seven simultaneous recordings of dP/dt and RPR were obtained. The average value of RPR was 1303 ± 1009 mmHg/s and that of dP/dt was 1533 ± 840 mmHg/s. The correlation between RPR and dP/dt was with 0.85 (P<0.0001, Fig. 1). The correlation varied among pigs, with r ranging between 0.87 and 0.95 (all with P<0.0001) and slopes varying from 0.93 to 2.52. The slopes were statistically different for the various pigs. The results in the third pig are depicted in Figure 2, showing the results under different inotropic conditions. Figure 3 shows the different slopes in the fourth animal under dobutamine (A) and after ischaemia (B).
There was a significant correlation between the mean left atrial pressure and dP/dt ($r=0.28$, $P=0.002$), but not with RPR ($r=-0.02$, $P$ not significant). Multivariate analysis demonstrated that the correlation between RPR and dP/dt was significantly modified by left atrial pressure, so that upon inclusion of the mean left atrial pressure in the regression equation, the correlation improved slightly ($r=0.89$, $P<0.00001$). The regression equation is:

$$\text{RPR} = \frac{dP/dt}{1000} + 61 \text{ LAP} + 183$$

where LAP is the mean left atrial pressure, simultaneously registered with dP/dt.

The range of the colour area of the mitral regurgitation was from 4 to 12 cm$^2$, with a mean value of $7.13 \pm 1.6$ cm$^2$. No correlation was observed between the degree of mitral regurgitation and the values of RPR or dP/dt.

**Discussion**

Our study agreed with previous papers that described the possibility of estimating dP/dt non-invasively by using the formula of Bargiggia$^{[4,5]}$. It shows that the correlation between RPR and dP/dt exists under extreme conditions of contractility, similar to those that can be found in clinical practice, such as acute ischaemia. It also demonstrates that RPR is highly sensitive to changes in the inotropic state, even more than dP/dt. The changes in RPR were significantly bigger than those in dP/dt under conditions of strongly stimulated or severely depressed contractility. RPR exhibited higher variability during inotropic stimulation, as seen in Table 1, which was an indication of the apparently greater sensitivity of RPR. These greater variations can be explained by the nature of Bargiggia’s formula. It involves a hyperbolic function of the type $y=k/x$, where $k$ is a constant value (32 mmHg). Therefore, when values of $x$ are lower than $k$, small variations of $x$ generate very large changes in $y$. Thus, when the value of $\Delta t$ is 32 ms, RPR is 1000 mmHg/s. In this range, a decrease in $\Delta t$ of 2 ms generates an RPR increase of 66 mmHg/s. However, if the value of $\Delta t$ is 16 ms (RPR 2000 mmHg/s), the same 2 ms decrease in $\Delta t$ generates an RPR increase of 285 mmHg/s, i.e. more than four times as great.

The increased sensitivity of RPR to impaired contractility can also be explained by the fact that (as seen in Fig. 3) when systolic pressure is low, the velocity of 3 m/s is not reached until late, well after the aortic valve opening, so $\Delta t$ increases and RPR falls more than dP/dt, in relative terms.

**Limitations of RPR**

RPR can only be obtained in patients with mitral regurgitation, and not even in all cases. A record of
sufficient quality cannot be obtained in around 16% of cases[9]. Nevertheless, mitral regurgitation is commonly associated with cardiac pathology[7–11], and the use of contrast agents will surely make it easier to register the curve of insufficiency. Secondly, the need for Doppler alignment with the regurgitant flow can be an important limitation, since angles which are too large cause an underestimation of gradients. In our study this problem was minimized, since the method used to cause mitral regurgitation allowed us to modify the direction of the jet at will. Thirdly, by definition, RPR underestimates the value of \( \frac{dP}{dt} \), since RPR is the average value of the slope of the curve over an interval, and \( \frac{dP}{dt} \) is its maximum value. This underestimation can clearly be seen in Figure 1, except for pig 5. The magnitude of the underestimation depends on the value of the left atrial pressure, since left atrial pressure is one of the determinants of the gradient of pressure that causes the regurgitation. RPR is not calculated from a real curve of ventricular pressure, but rather from a gradient curve of ventriculo-atrial pressure. Changes in left atrial pressure can be completely ignored with respect to changes in left ventricular pressure at the onset of systole[9], although they have a greater influence later on, especially if mitral regurgitation is severe, producing V-waves. Finally, load conditions can affect the value of RPR. Experimental studies designed to demonstrate the influence of load on RPR are lacking. Theoretically, load conditions — especially preload[1,2] — would affect RPR in the same way they affect \( \frac{dP}{dt} \), since they both represent the same physiological phenomenon.

**Limitations of the Study**

The method we used to cause mitral regurgitation was selected because it was cheap, feasible and allowed us to provoke different degrees of insufficiency, but is not representative of a chronic mitral regurgitation. We preferred to change the contractility over a broad range of values in order to reduce the number of experimental animals needed, following the recommendations of the ethical committee for research. This was why we considered acceptable the repetition of the protocol with the fifth animal. The experimental phase of the study concluded when the objective was clearly reached, although more animals would have given more information for secondary objectives.

The influences of load or heart rate were not considered in the design of the study, because the objective was to compare the sensitivities of RPR and \( \frac{dP}{dt} \), and not to assess the influence of load on RPR. Left atrial pressure and the degree of mitral regurgitation were controlled in order to avoid haemodynamical instability.

Our study shows an influence of left atrial pressure on the correlation between RPR and \( \frac{dP}{dt} \). Since RPR is estimated during a definite period of the isovolumic phase, the left atrial pressure should have been measured during that period. This was not technically possible, and so the mean value of the left atrial pressure was used. This value is an estimate of filling pressures and is related to pre-load. This could be the reason why a correlation between atrial pressure and \( \frac{dP}{dt} \) was found, and could also explain the different slopes of the curves traced for each pig — particularly the fourth and the fifth, as can be noted in Figure 1. These two pigs had a mean value of atrial pressure of \( 6.6 \pm 2.4 \) and \( 4.5 \pm 1.7 \) mmHg, whereas pigs 1 and 2 showed greater values of \( 10.8 \pm 3.7 \) and \( 10.5 \pm 3.9 \) mmHg during the experiment. The slight effect of the influence of left atrial pressure on the correlation between RPR and \( \frac{dP}{dt} \) might be due to the fact that no measurements were made at extremely elevated atrial pressures. Nevertheless, in patients with markedly increased left atrial pressure, and depending on the ventricular function, it is possible that the determination of RPR might be more affected.

Since \( \frac{dP}{dt} \) is a parameter sensitive to pre-load[1,2] an influence of the degree of mitral regurgitation on both \( \frac{dP}{dt} \) and RPR was expected. This fact, which has recently been demonstrated by Broka et al.[12], was not found, possibly because of the narrow range of degrees of mitral regurgitation induced: from 4 to 12 cm\(^2\), with most of them (91 measurements) from 6 to 8 cm\(^2\). Another possibility was the relatively poor specificity of the method chosen — epicardial colour-coded Doppler. Other methods, such as PISA or the width of vena contracta, should have been used in a study aimed at assessing the influence of the severity of the mitral regurgitation. It is our opinion that these results cannot be extrapolated to the practical, non-invasive estimation of \( \frac{dP}{dt} \).

The previously described limitations can make RPR of doubtful value in comparing the ventricular performance between individuals, with different degrees of regurgitation and atrial pressures. However, these are also limitations for \( \frac{dP}{dt} \), and to a smaller degree affect the main use of \( \frac{dP}{dt} \) and the theoretical purpose of RPR, which is the assessment of linear changes in the same individual. For this purpose, our results demonstrate that RPR reflects directional changes of contractility with high fidelity.

**Practical Utility of RPR**

\( \frac{dP}{dt} \) is a parameter of contractility during the isovolumetric contraction phase that is very sensitive to changes in the inotropic state, and is relatively independent of afterload[1,2]. Thus, it is frequently used to assess directional changes of left ventricular performance in experimental studies. Its clinical use is limited because of the need for left ventricular catheterization, and it is of doubtful value when comparing the function among different individuals. A more frequent utilization of \( \frac{dP}{dt} \) might increase our knowledge of ventricular function, since it exhibits different dependence on load conditions than the more commonly used ejection-phase parameters[2,13]. The non-invasive assessment of \( \frac{dP}{dt} \) in
patients with MR offers an open window to the isovolumetric phase with a relatively simple method, such as the formula of Bargiggia et al.\textsuperscript{[15]} The practical applications of Doppler-derived dP/dt should be similar to those of invasive dP/dt. RPR has proven to be a good predictor of left ventricular function after mitral valve replacement for treatment of mitral regurgitation\textsuperscript{[14]}, where parameters of ejection phase, such as ejection fraction (EF), have failed in predicting post-surgical ventricular function. In patients with dilated cardiomyopathy, with elevated afterload reflected by increased end-systolic stress, RPR exhibits no correlation with stress, whereas the EF is clearly influenced by afterload\textsuperscript{[13]}. Despite these early demonstrations of the possible usefulness of RPR, it was necessary to determine whether RPR had a sensitivity similar to that of dP/dt to changes in the inotropic state, which is in fact the main practical application of dP/dt.

In conclusion, RPR is a non-invasive estimation of dP/dt that is highly sensitive to changes in the inotropic state. It correlates well with the invasive value of dP/dt even in extreme conditions of contractility, whether increased or depressed. Despite its limitations, it could be useful to include the estimated dP/dt in clinical monitoring of changes in contractility, as well as in clinical research studies.

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**References**