Doppler echocardiographic and electrocardiographic atrioventricular time intervals in newborn infants: evaluation of techniques for surveillance of fetuses at risk for congenital heart block

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KEYWORDS: congenital heart block; Doppler; ECG; echocardiography; fetus; newborn

ABSTRACT

Objective To evaluate one novel and two previously reported Doppler flow velocimetric techniques to estimate atrioventricular (AV) time intervals, suggested to be useful for early identification of fetuses at risk for congenital heart block.

Methods In 22 newborn infants, Doppler tracings were obtained from the mitral valve/aortic outflow and the superior vena cava/ascending aorta, as an ECG was recorded simultaneously. AV time intervals were measured using the onsets of the mitral A-wave/aortic outflow (MV-Ao), superior vena cava a-wave/aortic flow (SVC-Ao), and mitral A-wave/mitral valve closure (MV) as indirect markers of electrical atrial/ventricular activation.

Results Close positive linear relationships to the electrocardiographic PR interval were demonstrated for the MV-Ao ($r = 0.82, S_{y/x} = 7.4$ ms), SVC-Ao ($r = 0.85, S_{y/x} = 6.8$ ms), and MV ($r = 0.92, S_{y/x} = 3.8$ ms) approaches. Both techniques using the aortic flow to indicate ventricular activation overestimated the PR interval: the MV-Ao by $+32 \pm 7.7$ ms (mean $\pm$ SD) and the SVC-Ao approach by $+22 \pm 7.0$ ms. The new MV approach using mitral closure for the same purpose did not overestimate the PR interval, but there was a trend towards underestimation of the PR intervals as time intervals increased.

Conclusions When systematic differences between echocardiographic and electrocardiographic AV time intervals are compensated for, all three techniques are useful to get indirect estimates of the PR interval. As MV recordings only need insonation of a single valve, and are thus easier to obtain, this technique may be of value as a first screening method to identify fetuses in need for further surveillance. In cases with AV time prolongation the SVC-Ao method seems superior. Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Congenital heart block without cardiac malformation (CHB) can develop after placental transfer of maternal anti-SSA/Ro and anti-SSB/La autoantibodies. Women with these antibodies are commonly diagnosed as having Sjögren’s syndrome, systemic lupus erythematosus or rheumatoid arthritis. With circulating Ro and/or La antibodies in the maternal serum there is a 2–5% risk of having a child with CHB, while the risk is 12–25% of having a second child with CHB. More recent studies suggest that the risk is higher in women in whom the anti-Ro activity is targeted at the 52-kd component of the antigen rather than the 60-kd component, especially for those women in whom it is directed at amino acids 200–239 of the 52-kd protein.

CHB is usually diagnosed at 18–24 weeks of gestation, when it is already complete and causing fetal bradycardia. A complete heart block is commonly considered to be permanent. However, in fetuses diagnosed with second-degree and a single recent case with third-degree atrioventricular (AV) block, an improvement in AV conduction was obtained by maternal treatment with fluorinated glucocorticoids.

Based on the assumption that CHB progresses gradually, starting with a first-degree AV block, measurement
of AV time intervals on Doppler echocardiographic tracings has been suggested as a method for the surveillance and early detection of fetuses at risk for CHB. Reference values have been established and, using these techniques, results were obtained recently supporting the idea that CHB is a disease that develops gradually.

Standard fetal echocardiographic techniques can be used to identify atrial and ventricular depolarization indirectly by their mechanical (M-mode) or hemodynamic (Doppler) consequences. Experimental studies have demonstrated the superiority of Doppler compared with M-mode for measuring fetal AV time intervals and thus for diagnosing first-degree AV block. Doppler echocardiographic signs of first-degree AV block have been confirmed in two single fetuses by the use of magnetocardiography. To the best of our knowledge, no other attempts have been made to compare AV time intervals on Doppler tracings with magnetocardiographic or electrocardiographic (ECG) measurements in the human fetus, and we are aware of only two studies in any population which have validated the Doppler technique against time-interval measurements on ECG tracings. In a study of ten newborn infants, AV time intervals obtained by recording simultaneously velocities in both the mitral valve and the aortic outflow, did not differ statistically from the ECG-derived PR interval. In another study on six exteriorized fetal lambs, AV time intervals obtained by recording simultaneously velocities from the superior vena cava (SVC) and the ascending aorta systematically overestimated the PR interval.

As these two methods use the onset of aortic outflow as a marker of ventricular activation, the early systolic phase of isovolumetric contraction will be included in the AV time measurements. To avoid this potential source of error in the estimation of PR intervals, we designed a new AV time interval that did not include the isovolumetric contraction time (ICT). The aim of this study was to evaluate this novel approach, as well as the two previously reported Doppler flow velocimetric methods suggested to be of importance in the surveillance of pregnancies known to be at risk for fetal CHB.

METHODS

Lacking a reliable method to record fetal ECGs we decided to perform our study on newborn infants, in whom simultaneous Doppler and ECG tracings could be obtained easily. We studied 22 newborn infants at a mean age of 2.9 (range, 1–7) days. Their mean birth weight was 3332 (range, 2190–4255) g, and they were born at term with an uneventful perinatal history. Both parents gave informed consent to have their baby examined, and the study was approved by the ethics committee at the Karolinska Hospital.

All cardiac examinations were performed by the same examiner using a Sequoia ultrasound system with a 7V3-MHz transducer (Acuson Computed Sonography, Mountain View, CA, USA). A complete pediatric echocardiographic examination, including Doppler examination of all valves and major vessels, was performed in all infants, demonstrating no abnormalities in cardiac structure or function. The ductus arteriosus was totally closed in all but two babies, in whom it was nearly closed and of no hemodynamic significance.

AV time intervals were estimated by three different measurements from Doppler recordings obtained at two different locations. Briefly, pulsed Doppler recordings were made with the transducer in an apical position, with the sample volume placed in the left ventricle at the junction of the anterior leaflet of the mitral valve and the left ventricular outflow tract, and with the sample gate sufficiently wide so as to encompass both the mitral inflow and the aortic outflow. The second recording was obtained from a slightly rotated sagittal, subcostal view, with the ascending aorta anterior to the SVC in a longitudinal axis. The sample gate was wide enough to include velocity information from both vessels. The angle of insonation was maintained within 30°. Both Doppler and precordial ECG tracings were recorded simultaneously on the ultrasound machine with a sweep speed of 100 mm/s, and recordings were stored digitally for later analysis. Tracings and measurements are defined in Figure 1.

All measurements were performed using the leading edge principle. On the recording from the mitral valve and aortic outflow, AV time intervals were measured as described previously, from the intersection of the mitral E- and A-waves to the onset of the ventricular ejection wave in the aortic outflow (MV-Ao). We also quantified a time interval starting with the same event but ending at the closure of the mitral valve (MV), which represents the first mechanical sign of ventricular systole in these Doppler tracings. The difference between these two measurements, the ICT, was calculated by subtraction. The method used to calculate AV time intervals from recordings of the SVC and ascending aorta has also been described previously. Briefly, this time interval was measured from the beginning of the retrograde venous a-wave in the SVC to the beginning of the aortic ejection wave (SVC-Ao).

ECG tracings were used to assess the PR interval as well as the time for a complete cardiac cycle, the RR interval. The ECG was also used to quantify the time delay from the start of the PR interval to the start of the AV interval on the Doppler tracings (PA-delay), as well as the time delay between their respective endings (RV-delay). All time intervals were measured on three cardiac cycles and averaged.

To evaluate the agreement between observers for the different Doppler approaches, a second qualified pediatric cardiologist independently selected three complexes for analysis and repeated all AV time-interval measurements.

Statistical analysis was performed using the computer package Statistica 6.0 (StatSoft, Tulsa, OK, USA). Shapiro–Wilk’s test was used to verify normality. Relationships between AV time intervals on Doppler tracings and the PR interval on ECG tracings were
investigated using linear regression and the F-test. To assess the agreement between these time intervals we used plots as suggested by Bland and Altman\textsuperscript{25,26}, and the t-test for dependent samples. To test the agreement between measurements made by the two independent observers a one-way ANOVA was used to estimate the various components of variance required to calculate the within-subjects coefficients of variation and repeatability, as well as the intraclass correlation coefficient (ICC)\textsuperscript{27,28}. The level of significance was set at $P < 0.05$.

**RESULTS**

Doppler and ECG tracings were obtained simultaneously in all 22 infants, except for one in whom breathing and body movements prevented an acceptable recording from the mitral valve and aortic outflow.

Highly significant positive linear correlations between AV time intervals and the ECG PR interval were found for all three Doppler techniques. These relationships are illustrated together with their 95\% confidence limits for individual observations in Figure 2. Interestingly, the best linear fit was obtained for the novel MV approach ($r = 0.92$, $S_{y/x} = 3.8$ ms), compared with the MV-Ao ($r = 0.82$, $S_{y/x} = 7.4$ ms) or SVC-Ao ($r = 0.85$, $S_{y/x} = 6.8$ ms) approaches. A systematic overestimation of the PR interval with the MV-Ao (+32 ± 7.7 ms (mean ± SD), $P < 0.001$) and SVC-Ao approaches (+22 ± 7.0 ms, $P < 0.001$), evident in Figure 2, is demonstrated more clearly in Figure 3. This overestimation or bias is illustrated with 95\% limits of agreement (mean ± 2 SD) in these plots of the difference against the mean value of the corresponding AV and PR intervals (Figure 3a and c); linear regression did not demonstrate any change in the differences when the average value of the two measurements increased. Time intervals obtained with the novel MV approach, however, did not show the same systematic overestimation. On the other hand, there was a trend towards shorter AV time intervals relative to PR intervals, when the time intervals increased. This trend in the bias is illustrated in Figure 3b by the linear regression ($y = 30 - 0.36x$, $S_{y/x} = 4.6$ ms, $r = 0.66$, $P < 0.005$) and 95\% confidence limits for individual observations, which could be expected to be a better estimate of the limits of agreement in this situation. No linear relationships were found between either AV time or PR intervals, and RR intervals.

When compared directly, AV time intervals obtained with the MV-Ao approach were significantly longer than were those recorded with the SVC-Ao approach, which in turn were significantly longer than were those from the MV approach (Table 1). We also found that the electrohemodynamic delay from the start of the PR interval to the start of the AV interval (PA-delay) was approximately 13 ms shorter for the MV-Ao compared with the SVC-Ao approach, which was highly significant ($P < 0.001$). The ICT, isovolumetric contraction time; PA- and RV-delay, time delay between start of PR interval and that of AV interval, and time delay between their respective endings.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Doppler velocity records and electrocardiographic (ECG) tracings. (a) A recording from the mitral valve (upward) and aortic outflow (downward). The atrioventricular (AV) time interval was measured from the intersection of the mitral E- and A-waves (A) to the onset of the aortic ejection wave (V, second line) for the MV-Ao method, or to the closure of the mitral valve (V, first line) for the MV approach. (b) A recording from the superior vena cava (upward) and aorta (downward). The AV time interval was measured from the beginning of the retrograde venous a-wave (A) to the beginning of the aortic ejection wave (V). The PR intervals were measured from the onset of the P-wave (P) to the beginning of the QRS (R) complex on the ECG.

<table>
<thead>
<tr>
<th>Method</th>
<th>PR interval (ms)</th>
<th>RR interval (ms)</th>
<th>PA-delay (ms)</th>
<th>AV time (ms)</th>
<th>ICT (ms)</th>
<th>RV-delay (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV-Ao</td>
<td>95 ± 13.2</td>
<td>526 ± 61.5</td>
<td>39 ± 6.4</td>
<td>127 ± 12.7</td>
<td>35 ± 6.0</td>
<td>70 ± 6.7</td>
</tr>
<tr>
<td>MV</td>
<td>96 ± 13.0</td>
<td>545 ± 72.7</td>
<td>52 ± 9.6*</td>
<td>92 ± 9.4†</td>
<td>118 ± 12.9*</td>
<td>72 ± 7.3</td>
</tr>
<tr>
<td>SVC-Ao</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* $P < 0.001$ (MV-Ao vs. SVC-Ao), †$P < 0.001$ (SVC-Ao vs. MV). PR and RR intervals were measured on the ECG and AV time intervals on the Doppler tracing. ICT, isovolumetric contraction time; PA- and RV-delay, time delay between start of PR interval and that of AV interval, and time delay between their respective endings.

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with the SVC-Ao approach. Thus, the acceleration of mitral inflow to the left ventricle (A-wave) precedes the reversal of flow (a-wave) in the SVC, explaining why MV-Ao time intervals were systematically longer compared with those from the SVC-Ao.

The results of the analysis of the agreement between time measurements made by the two observers are presented in Table 2. There was a small but significant difference (2.3 ± 2.5 ms, \( P < 0.01 \)) between investigators for the MV-Ao approach. Otherwise no systematic differences were demonstrated. The interobserver variability was low for all three methods, when analyzed both against other sources of variation (ICC, 0.95–0.96) and against the mean value of the observations (coefficient of variation (CV), 2.0–2.5%). The repeatability coefficients, estimating the maximum differences likely to occur in 95% of repeated measurements, also suggested good agreement between the observers.

**DISCUSSION**

This study was conducted to evaluate one new and two previously reported Doppler flow velocimetric methods designed to identify fetuses with first-degree AV block. When comparing AV time intervals with ECG PR intervals, strong positive linear relationships were demonstrated for all three methods. The MV-Ao approach systematically overestimated the PR interval to a degree (+32 ± 7.7 ms) that was approximately the same as the ICT. By using the novel MV approach and directly excluding the ICT from the AV measurement, systematic overestimation of the PR interval was thus avoided. The SVC-Ao measurements also included the ICT, but as a consequence of a later onset of the flow reversal (a-wave) in the SVC compared with the start of accelerated inflow to the left ventricle (A-wave), AV time intervals

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**Table 2** Agreement between atrioventricular (AV) time measurements made by two observers

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD (ms)</th>
<th>ICC</th>
<th>CV (%)</th>
<th>( \tau ) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMV-Ao</td>
<td>2.3 ± 2.5*</td>
<td>0.96</td>
<td>2.0</td>
<td>7.0</td>
</tr>
<tr>
<td>ΔMV</td>
<td>0.0 ± 2.0</td>
<td>0.95</td>
<td>2.2</td>
<td>5.7</td>
</tr>
<tr>
<td>ΔSVC-Ao</td>
<td>−0.5 ± 2.9</td>
<td>0.95</td>
<td>2.5</td>
<td>8.1</td>
</tr>
</tbody>
</table>

\* \( P < 0.01 \). CV, coefficient of variation; ICC, intraclass correlation coefficient; \( \tau \), repeatability coefficient.
recorded from the SVC-Ao overestimated the PR intervals by approximately 10 ms less than did those obtained with the MV-Ao approach. We can only speculate as to why this would be, but a reasonable explanation could be that more time is needed to cause a reversal of flow in the SVC, compared with the time needed to accelerate flow in the same direction as in the mitral valve. AV time intervals obtained with the MV approach showed the best agreement with PR intervals, but there was a trend of underestimation of the PR interval as these time intervals became longer. Higher heart rates have been demonstrated to result in increasing fusion of the E- and A-waves in the mitral valve, overlapping the beginning of the A-wave and leading to an artifactual shortening of the AV time interval\(^2\). We cannot explain our observation of an increasing heart rate. However, as the PR interval gets longer with no associated decrease in heart rate, the A-wave will have an earlier start in relation to the E-wave, in turn causing increasing overlapping of the E-wave and an artifactual shortening of the A-wave. This phenomenon should also affect the MV-Ao measurements, but is probably hidden in the increased variability induced by including the ICT. Still, the artifactual shortening of the mitral A-wave might explain why the slopes of the regressions presented in Figure 2 are less for the MV (b = 0.64) and MV-Ao (b = 0.79) approaches compared with the SVC-Ao (b = 0.85) recordings.

As Doppler recordings of AV time intervals are usually made for comparison with reference data obtained by the same technique, with no intention of numerically estimating the PR interval, systematic differences in the agreement between AV time and PR intervals will not represent a methodological problem. Thus, for comparing our methods a more informative analysis would be to investigate the degree to which observations fluctuate around the mean value. For the MV-Ao and SVC-Ao approaches, this fluctuation, described as the 95% interval of agreement, was approximately ±15 ms and ±14 ms, respectively (Figure 3). For the MV technique, a somewhat smaller 95% confidence interval of roughly ±9 ms was calculated from the regression. However, this variability became more or less the same (CV, 5–6%) when taking into account that time intervals measured with the MV approach were shorter than were those obtained with the two other techniques.

Speculating that the relative impact of methodological errors might increase when measuring the shorter MV time intervals, a second independent observer repeated all measurements. Finding excellent agreement between observers for all approaches this concept could not be confirmed. The highest degree of variation was actually demonstrated for the SVC-Ao approach, due probably to problems with identifying the precise start of the venous a-wave in the SVC. The reversal of flow in the SVC is not an instantaneous phenomenon occurring at exactly the same time over the cross-section of the vessel, resulting in a less sharp start of the a-wave, and the SVC flow velocity waveform can be affected by breathing. Notably, other investigators have demonstrated better interobserver reliability for the SVC-Ao than the MV-Ao approach in human fetuses, who are routinely studied during apnea\(^2\).

Only few investigators have compared AV time intervals from Doppler recordings with measurements of the PR interval from ECGs. In the study of ten newborn infants, AV time intervals obtained by the MV-Ao approach were not significantly different from PR intervals measured from ECG recordings made, at a paper speed of 25 mm/s, within minutes of the Doppler recording\(^1\). In our study on twice the number of newborns, the ECG was recorded simultaneously with the Doppler tracing at a sweep speed of 100 mm/s and PR intervals were found to be systematically shorter than were AV time intervals measured on recordings from both the MV-Ao and SVC-Ao approaches. Our finding is, however, in accordance with the experimental study on exteriorized fetal lambs, demonstrating SVC-Ao AV time intervals exceeding concomitantly recorded PR intervals by 33 ms\(^2\).

Our study was performed on newborn babies with the purpose of evaluating a Doppler echocardiographic approach suggested for surveillance of the midterm fetus. In the newborn period hemodynamic conditions are changing constantly and to minimize this problem we did not include babies in our study until they were at least 1 day old and were without any significant ductal shunt. The AV time intervals obtained in our study were very similar to those recorded previously in the term fetus\(^1\), suggesting that differences in loading conditions between newborns and fetuses did not have any systematic effect on ICT or AV time intervals. Breathing and ongoing changes in loading conditions might, however, still have affected the variability of our measurements. Hence, our approximations of variability in the newborn are probably overestimates of the corresponding variables in the fetus, especially for venous profiles as used by the SVC-Ao approach.

In summary, our data have demonstrated close positive relationships between AV time intervals on Doppler flow velocimetric tracings and the PR interval on ECGs. Previously described techniques using the aortic outflow to identify the start of ventricular contraction systematically overestimated the PR interval. Using a novel approach, denoting the start of the mitral valve closure as the onset of ventricular contraction we avoided this overestimation. Assuming that measurements made in the clinical setting are compared to references obtained with the same technique, our results indicate that all three Doppler methods will have acceptable variability. High-quality records from a single valve like the MV are usually easier to obtain than are those with the MV-Ao or SVC-Ao approach, which encompass two valves or vessels. AV time intervals obtained with the MV approach should also be less affected by systolic ventricular performance. However, as time intervals increased, there was a trend towards underestimation of the PR intervals with this approach. To validate this potential methodological problem, studies on the human fetus are in progress.
Thus, our data suggest that the novel MV approach could have a place as a more widely used screening method to decrease the number of fetuses in need of closer surveillance for CHB. As the SVC-Ao approach does not suffer from artifactual shortening of the A-wave, this method would have advantages over both the MV and the MV-Ao methods in fetuses with AV time prolongation and tachycardia.

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