Giant Fetal Magnetocardiogram P Waves in Congenital Atrioventricular Block
A Marker of Cardiovascular Compensation?

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Background—Cardiogram signal amplitude is a key index of hypertrophy but has not been investigated extensively in utero. In this study, magnetocardiography was used to assess P and QRS amplitude in normal subjects and subjects with fetal arrhythmia.

Methods and Results—The study cohort consisted of 68 normal fetuses and 25 with various arrhythmias: 9 reentrant supraventricular tachycardia (SVT), 2 ventricular tachycardia (VT), 2 sinus tachycardia, 2 blocked atrial bigeminy, 2 congenital second-degree atrioventricular (AV) block, and 8 congenital complete AV block. Subjects with congenital AV block, all presenting with bradycardia, showed large QRS amplitude, exceedingly large P-wave amplitude, and long P-wave duration. The 2 subjects with VT, both with poor ventricular function, also exhibited large P waves. SVT was associated with only moderate signal amplitude elevation.

Conclusions—The data imply that AV block in utero is accompanied by hypertrophy, which is more pronounced for the atria than the ventricles. We hypothesize that the hypertrophy results from a compensatory response associated with regulation of cardiac output and is likely to be observable in other arrhythmias and disease states. Magnetocardiography may be more sensitive than fetal echocardiography for detection of atrial hypertrophy in utero. (Circulation. 2004;110:2097-2101.)

Key Words: arrhythmia • heart block • hypertrophy • electrophysiology • tachycardia

The fetal magnetocardiogram (fMCG) is the magnetic analog of the fetal ECG. Although it is similar to fetal ECG in many respects, fMCG provides better signal quality as the result of the favorable transmission properties of magnetic signals. A number of recent reports show fMCG to be a highly effective means of diagnosing fetal arrhythmia. In cases of life-threatening fetal arrhythmia, it can improve clinical management and enhance transitional care to the newborn period.

Assessment of signal amplitude is an important aspect of cardiogram interpretation, largely because elevated amplitude is a primary indicator of hypertrophy; however, fMCG signal amplitude has not been used extensively in rhythm evaluation for several reasons. First, signal amplitude has not been adequately characterized even in normal fetuses. Prior normative studies have focused mainly on measurement of cardiac waveform intervals and the success rate of QRS detection. Assessment of P-wave amplitude has not been reported. Second, interpretation of signal amplitude is likely to be difficult. Compared with postnatal cardiograms, the fMCG exhibits highly variable signal amplitude as the result of its strong dependence on such factors as gestational age, fetal position, and detection coil configuration. Despite this, Horigome et al succeeded in showing that QRS amplitude is significantly increased in cardiomegaly. In addition, our group has demonstrated the utility of transient signal amplitude variations for assessing fetal breathing movements and the association of fetal truncal movement with onset and termination of fetal supraventricular tachycardia.

In a prior case study of autoimmune-associated congenital complete atrioventricular block (CCAVB), we observed that the P-wave amplitude was unusually large but we were unable to determine the underlying cause. With further study of CCAVB and other types of fetal arrhythmia, it has become apparent that these conditions are often associated with elevated signal amplitude. In this study, we measured the amplitudes of the QRS complex and the P wave and compared these data in normal subjects and subjects with fetal arrhythmia.

Methods

Our institutional human subjects committee approved the experimental protocol. The subject cohort consisted of 68 normal volunteers, 9 fetuses with reentrant supraventricular tachycardia (SVT), 2 with ventricular tachycardia, 2 with sinus tachycardia, 2 with blocked
atrial bigeminy, 2 with second-degree congenital atroventricular block (2° AVB), and 8 with CCAVB. The gestational ages ranged from 14 to 40 weeks for the normal subjects and 17 to 39 weeks for subjects with fetal arrhythmia. One subject with CCAVB had structural heart disease; the other 9 subjects with congenital second- or third-degree AV block (CAVB) had positive test results for maternal Sjögren’s syndrome A antibodies, and 8 of them received dexamethasone therapy. Antiarrhythmic drug therapy was being administered at the time of study in 4 patients with SVT: 3 were receiving digoxin and 1 was receiving digoxin and amiodarone. Serial measurements were made on 38 of the normal subjects and 11 of the patients with arrhythmia.

The fetal MCG recordings were made with a 37-channel, first-order gradiometer (Magnes, 4D Neuroimaging) in a high-permeability magnetically shielded room (Lindgren RF Enclosures). At least three 10-minute recordings were taken from each subject at different probe positions to ensure sufficient coverage to record the maximum signal amplitude. Peak-to-peak P and QRS amplitudes were measured in the channel with largest P wave and the channel with largest QRS complex. Averaging was used to improve the signal-to-noise ratio, using procedures described previously. We also computed P/QRS ratio because many of the extrinsic factors that cause signal amplitude variation, such as position and orientation of the fetal heart, affect both P-wave and QRS amplitude. The T wave, which could not be resolved easily in many subjects, was not assessed. P-wave duration, taking the longest duration over all channels, was measured in a subset of subjects at 28 to 32 weeks gestation to reduce the confounding effect of gestational age in comparing P-wave duration in CAVB versus normal subjects.

Linear regression was used to assess the dependence of the amplitude parameters on gestational age. The regression lines of the normal and arrhythmia subjects were compared through the use of ANCOVA. The 95% prediction interval was computed for the normal group. P-wave duration in CAVB versus normal subjects was compared by means of a 2-tailed unpaired test. For all statistical tests, the level of significance was assumed to be $P<0.05$.

Postnatal 12-lead ECGs were obtained within 24 hours of delivery.

**Results**

**Normal Subjects**

The main study data are presented in Figure 1, which shows QRS and P-wave amplitude as a function of gestational age. As expected, linear regression analysis of the normal subject data showed a statistically significant increase with gestational age for QRS amplitude ($n=142, r^2=0.2831, P<0.0001$) and P-wave amplitude ($n=142, r^2=0.1916, P<0.0001$). Figure 1, C and D, respectively, show that the P/QRS ratio was $\approx 0.1$ for the channel with largest QRS amplitude and $\approx 0.2$ for the channel with largest P-wave amplitude. These ratios were nearly constant throughout gestation.

**Subjects With Bradyarrhythmia**

The most striking observation was the exceedingly large P waves seen in every case of CAVB (Figure 2 and Figure 3B). This phenomenon was present regardless of whether or not block was complete, structural disease or maternal SSA antibodies were present, or dexamethasone therapy was given. In several subjects with CAVB, the amplitude of the P wave was transiently much greater than that of the QRS complex (Figure 2), whereas none of the normal subjects ever showed this.

The slope of the P-wave regression line in Figure 1B was significantly greater in CAVB than in normal subjects ($P<0.0001$). Overall, the percent elevation of the P wave was $\approx 200\%$. This divergence from normal occurred earlier in gestation than did divergence of the QRS, did not moderate over time, and was most prominent at late gestational ages. The slope of the regression line for QRS amplitude was also elevated in CAVB versus normal subjects ($P<0.0006$) but not as much or as early as for P-wave amplitude, as evidenced by the high P/QRS ratio of the subjects with CAVB (Figure 1, C and D).

Bradycardia was present in all subjects with CAVB. Mean heart rate ranged from 50 to 80 bpm in subjects with CCAVB and from 63 to 110 bpm in 2° AVB, except for one subject with 2° AVB block (open circles in Figure 3), who showed predominantly first-degree block with mean heart rate 135 bpm during the second of five sessions. Although heart rate in that session was normal, P and QRS amplitudes remained elevated, suggesting that this phenomenon is not a bradycardia-specific acute change. Despite the intuitive presumption that lower heart rate should increase amplitude, no correlation could be demonstrated among the small number of subjects with CAVB between heart rate and the severity of P-wave amplitude elevation. During ultrasound examination, atrial and ventricular hypertrophy were noted in one patient and ventricular hypertrophy was noted in another (open circles and closed upright triangles, respectively, in Figure 3, A and B).

In addition to the subjects with CAVB, fetuses at 20 and 23 weeks’ gestation (asterisks in Figure 1) had bradycardia with mean rate 83 and 81 bpm, respectively, caused by blocked atrial bigeminy. P-wave amplitude was moderately elevated in both fetuses. The first fetus returned for a second session at 25 weeks’ gestation. Normal sinus rhythm was present throughout, but P-wave amplitude remained moderately elevated.

The table compares P-wave duration at 28 to 32 weeks’ gestation between a group of subjects with CAVB and two groups of normal subjects: a group with P-wave amplitude near the regression line for normal subjects and a group with large P-wave amplitude, near or above the 95% prediction interval. P-wave duration in the subjects with CAVB was significantly prolonged compared with both groups, with $P=0.003$ and $P=0.001$, respectively, for the comparisons with the first and second group.

**Subjects With Tachyarrhythmia**

The 2 subjects with sinus tachycardia had normal P-wave amplitude, but the 2 subjects with ventricular tachycardia, both with poor ventricular function, showed elevated P-wave amplitude (Figure 1B). For the subjects with SVT, the signal amplitudes were larger than for normal subjects (Figure 1, A and B), but the increase was statistically significant only for the P-wave ($P<0.005$) and not for the QRS complex. In patients with intermittent SVT, QRS and P-wave amplitudes were similar in SVT and normal sinus rhythm (inverted triangles in Figure 1), suggesting that the increased amplitude is not due to eccentric contractions and is not an acute tachycardia rate–dependent phenomenon.

**Discussion**

The main findings of this study are that CAVB in utero is associated with increased QRS amplitude, greatly increased P-wave amplitude, and long P-wave duration and that other forms of fetal arrhythmia are associated with lesser degrees of amplitude elevation. The magnitude and consistency of the
P-wave amplitude elevation in CAVB was remarkable. The overall percent increase was ~200%, and in every instance the P-wave amplitude was at or above the 95% prediction interval for normal subjects. These trends were evident early and increased progressively during gestation.

The intrinsic causes of increased cardiogram amplitude and duration are similar for MCG and ECG and include hypertrophy, hyperplasia, chamber enlargement, and increased contractility. Hereafter, we refer only to hypertrophy, while recognizing that all or several of the above factors may be involved.

After birth, tall P waves are a common ECG finding in patients with CAVB, and several studies show dilated cardiomyopathy to be a cause of morbidity and mortality, yet the onset, prevalence, and underlying causes of hypertrophy in CAVB have not been extensively characterized. Our findings imply that 2°AVB and CCAVB are uniformly accompanied by hypertrophy that is detectable in utero very soon after disease onset and is more pronounced and occurs earlier for the atria than the ventricles.

The most likely cause of large P waves in the subjects with CCAVB as well as the subjects with bradycardia caused by blocked atrial bigeminy is hypertrophy resulting from a compensatory response to low heart rate. When heart rate falls, the baroreceptor reflex attempts to restore arterial pressure through such measures as heart rate acceleration and vasoconstriction. Vasoconstriction elevates ventricular filling (venous) pressure, thereby increasing stroke volume by means of the Frank-Starling mechanism. In the fetus, however, the low compliance of the ventricles reduces the

Figure 1. Variation with gestational age of A, QRS amplitude; B, P-wave amplitude; C, P/QRS ratio for the channel with largest QRS; and D, P/QRS ratio for the channel with largest P wave. Normal subjects are indicated by solid circles. Patients with fetal arrhythmia are indicated by open symbols defined in the figure legend. Signal detection failed in 10 cases, indicated by crosses on the x-axis at the corresponding gestational age. Regression lines are derived from normal subject data and were computed two different ways. The first (solid line) was to exclude subjects from whom a signal could not be detected. The second (broken line) was to include them and to assign them signal amplitude zero. These serve as upper and lower bounds for the true regression line. The 95% prediction interval is indicated by thin dashed lines. Also shown are the regression lines for subjects with SVT and CAVB.
effectiveness of the Frank-Starling mechanism, and it is believed that regulation of cardiac output is accomplished primarily through control of heart rate. However, in CCAVB, the ability to increase heart rate is severely limited; thus, the ability to increase stroke volume becomes crucial. In this circumstance, compensation by means of the Frank-Starling mechanism assumes a greater role and, combined with the low compliance of the ventricles, could cause venous pressure to rise precipitously. If the atria are more compliant than the ventricles, then they might be more susceptible to distention and subsequent hypertrophy, consistent with our observations. In addition to low ventricular compliance, an additional factor specific to the fetus is that the atria are connected and effectively form a single chamber; thus, systemic venous pressure acts on the left as well as the right atrium. Adult studies show that right atrial hypertrophy mainly elevates P-wave amplitude, whereas left atrial hypertrophy prolongs P-wave duration. The amplitude and duration of the P waves in our subjects with fetal CAVB show parallel increases, demonstrating that the atria respond as a single unit.

According to the above theory, fetuses with CCAVB would be particularly susceptible to hypertrophy because of their limited ability to increase cardiac output through heart rate acceleration; however, hypertrophy may also occur at higher heart rates if cardiac output is compromised as the result of poor ventricular function or other causes. In fetuses with VT, the elevated end-diastolic pressures generally associated with rapid VT could cause a compensatory response similar to that seen in bradycardia. Because the reduction in cardiac output with VT is much greater than with SVT, the fetus must compensate quickly and to a much greater extent.

Our findings imply that fMCG may provide a sensitive early marker for atrial hypertrophy in utero. Detection of atrial hypertrophy with ultrasound is difficult because the thickness of the fetal atrium is <1 mm; also, the atria are imaged less

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**Figure 2.** Representative tracings depicting P-wave amplitudes in normal subjects and subjects with CCAVB and 2°AVB. Gestational ages of subjects in the top three tracings are 32 to 33 weeks. The fourth tracing, taken from a subject with CCAVB at 36 weeks' gestation, shows an example in which the P wave was transiently larger than the QRS complex. Postnatal ECGs (bottom) are from subjects in the second and third tracings above. In the left tracing, note atrial situs inversus in a subject with complex congenital heart disease; in the right tracing, note first-degree AV block with left QRS axis deviation. Both tracings show prominent P waves.

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**Figure 3.** A, QRS amplitude, and B, P-wave amplitude of patients with congenital heart block. Solid symbols correspond to subjects with congenital complete heart block who received dexamethasone (CCAVB+dex). Open symbols correspond to two subjects with incomplete congenital heart block who received dexamethasone (CAVB+dex), one subject with CCAVB who declined dexamethasone therapy (CCAVB), and one subject with CCAVB and structural disease (CCAVB+struc). Symbols on the x-axis indicate the initiation of dexamethasone therapy. Regression lines from normal subject data are plotted for reference.
quantitatively than the ventricles during routine clinical examination. In several subjects, however, we asked the sonographer to look for atrial hypertrophy, but it was seen in only one case, in which unusually thickened atrial muscle trabeculae were identified. With further study, using both technologies, more sensitive fetal echocardiographic markers of atrial hypertrophy can perhaps be identified.

The signaling pathways associated with the adaptive response of hypertrophy have been the focus of intense study, and recent work by Romano and colleagues supports the idea that in the fetus the atria may adapt more rapidly to stress than the ventricles. Furthermore, triggering of hypertrophy in the mature heart is associated with a reversal of gene expression to a fetal pattern, with increased expression of atrial natriuretic peptide and β-myosin heavy chain and decreased expression of α-myosin heavy chain. A notable aspect of this study was the heterogeneity of the subjects with CAVB with respect to degree of block, presence of maternal SSA antibodies, and administration of dexamethasone therapy. Although the number of subjects in each category is low, the uniformity of hypertrophy in CAVB implies that none of these factors alone can account for our data. Of particular interest is the role of dexamethasone, which is now widely prescribed in cases of fetal heart block associated with autoimmune disease. Prior studies of premature infants exposed to high-dose steroid therapy have shown the rapid development of ventricular hypertrophy. Our study shows that hypertrophy is indeed present in CAVB but that dexamethasone is not the sole cause, that is, hypertrophy occurs even in its absence. Whether dexamethasone exacerbates hypertrophy in CAVB is an important question that requires further study. A similar inference can be made with regard to the effects of AV dissociation, which can cause atrial hypertrophy resulting from contraction of the atria against a closed AV valve. Clearly, hypertrophy occurs in CAVB even in the absence of AV dissociation. Furthermore, such “canon” A-wave contractions occur during SVT, yet P-wave amplitude in SVT was not as affected. Thus, AV dissociation cannot be the sole cause of atrial hypertrophy, although it may be a contributing factor.

We have previously shown that precise electrophysiological diagnosis can be made in utero using FMCG. This study suggests that the addition of amplitude information may be useful in further risk-stratifying patients. In addition to arrhythmia, FMCG should be considered for study in disease states in which hypertrophy or cardiac insufficiency are likely to occur. This would include genetic conditions, renal anomalies, growth retardation, hydrops fetalis, myocarditis, diaphragmatic hernia, and congenital heart disease.

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### References
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