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Atrioventricular Conduction Time in Fetuses Assessed by Doppler Echocardiography

V. TOMEK[1], J. JANOUŠEK[1], O. REICH[1], J. GILÍK[1], R. A. GEBAUER[1], J. ŠKOVRÁNEK[1]

[1]Kardiocentrum and Cardiovascular Research Centre, University Hospital Motol, Prague, Czech Republic

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Summary

We performed measurement of mechanical atrioventricular conduction time intervals in human fetuses assessed by Doppler echocardiography and provided reference values. We found that atrioventricular conduction time interval was prolonged with gestational age and decreased with increasing fetal heart rate. No correlation between gestational age and heart rate was found. Using normal limits established by this study, mechanical atrioventricular interval >135 ms in the 20th week and/or >145 ms in the 26th week of gestation could be suspected of having the first-degree AV block. We compared reference values with fetuses of mothers with anti-SSA Ro/SSB La autoantibodies, being in risk of isolated congenital heart block development. One of 21 fetuses of mothers with positive autoantibodies was affected by prolonged atrioventricular interval according to the established limits, with sinus rhythm after the birth.

Key words

Atrioventricular block • Prenatal ultrasonography • Fetus • Doppler echocardiography

Corresponding author

V. Tomek, Kardiocentrum and Cardiovascular Research Centre, University Hospital Motol, V úvalu 84, 150 08 Prague 5, Czech Republic. Fax: +420 22443 2915 E-mail: viktor.tomek@fnmotol.cz

Introduction

Isolated congenital heart block is a rare but devastating condition with an incidence of 1 in 15000-20000 liveborns (Buyon *et al.* 1995). But it occurs in 2-5 % of pregnancies with anti-SSA/Ro and anti-SSB/La positive autoantibodies (Buyon *et al.* 1998). Complete atrioventricular block is considered to be irreversible, however, maternally administered corticosteroids may limit the progression of the first-degree or the second-degree atrioventricular (AV) block as described by anecdotal cases (Copel *et al.* 1995, Saleeb *et al.* 1999, Shinohara *et al.* 1999).

AV block may occur as the first sign of the conduction disorder (Askanase *et al.* 2002). However, a gradual development of atrioventricular block has mostly been described (Sonesson *et al.* 2004). Initially, normal heart rate with a prolonged AV conduction time interval may progress to a complete form of AV block. Dexamethasone given during pregnancy may achieve normalization of prolonged atrioventricular conduction time interval and averts the progression to complete heart block, which is irreversible (Sonesson *et al.* 2004, Friedman *et al.* 2008). The prophylactic treatment of all Sjögren´s positive pregnancies is not reasonable due to fetal side effects of corticotherapy (Costedoat-Chalumeau *et al.* 2003). The measurement of Doppler derived mechanical AV conduction time interval could identify affected fetuses within the first-degree AV block stage. Those fetuses might benefit from direct transplacental steroid administration to avoid progression to complete and irreversible AV block.

Some authors observed that the AV conduction time prenatally is independent of gestational age and heart rate (Glickstein *et al.* 2000), some others found a correlation between those variables (Andelfinger *et al.* 2001).

The purpose of this study was to establish reference values for mechanical atrioventricular conduction time intervals by Doppler echocardiography in fetus and to evaluate the correlation with gestational age and heart rate. Subsequently, mechanical AV conduction time intervals measured in normal fetuses were compared with those measured in pregnancies with positive SSA/SSB antibodies.

Methods

Study cohort

Over a period of three years (2007-2009) all fetuses of healthy pregnant women with structurally normal hearts referred to our laboratory because of a family history of congenital heart disease or because of previously suspected heart defect not confirmed by evaluation were included in the study (Group A, N=180). Each fetus was examined just once. The gestational age at evaluation varied from the 18th to the 39th week (median 25). The study protocol was evaluated and approved by the institutional ethical committee. Normal limits of mechanical PQ intervals were established. Finally, mechanical PQ intervals from fetuses of SSA/SSB-positive mothers examined in the period between 2003 and 2009 (Group B, N=21) were compared with normal limits as established in Group A.

Echocardiography technique

All pregnancies underwent transabdominal echocardiography revealing a normal heart structure and function by two-dimensional, colour and pulsed Doppler examination. Studies were performed on Vivid 7 (GE Medical Health Systems) using 2.5-8 MHz convex transducers. A physician experienced in prenatal echocardiography did every examination. The mechanical AV conduction time intervals were obtained from a four-chamber view tilted anteriorly to the outflow tract of the left ventricle. Pulsed Doppler sample volume was adjusted. The sample volume of pulsed Doppler was established in the width enabling to receive simultaneous traces from the mitral valve and left ventricular outflow tract (LVOT). The Doppler pattern of inflow and outflow traces was stored and measured offline. The mechanical AV conduction time interval was assessed as the interval between the onset of the mitral A-wave and the onset of the LVOT (V-wave). The time interval between A-wave and V-wave is equal to the onset of atrial and ventricular contraction and represents the mechanical AV conduction time interval (Fig. 1).

The same measurements of mechanical PQ interval were performed in the 20th and the 26th week in a group B consisting of SSA/SSB-positive pregnancies.

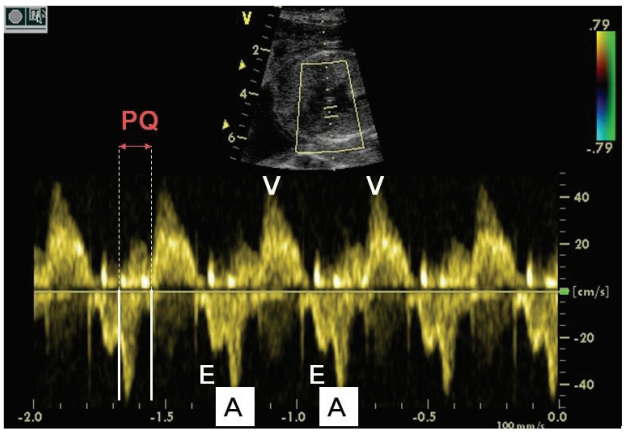

Fig. 1. Mechanical PQ intervals measured from modified four-chamber view. The simultaneous flow through the mitral valve (E- and A-waves) and the aortic valve (V-wave).

Statistical analysis

Data were analysed using SPSS 9.0 software. Continuous variables were expressed as mean or median as appropriate given by the data distribution pattern. Unpaired *t*-test or the Mann-Whitney rank sum test was used for comparison of patient groups. To evaluate the relation between the mechanical AV conduction time interval and heart rate and gestational age, linear regression models were used. The 1st and 99th percentile determined normal range. To increase the diagnostic specificity of first-degree AV block assessed by Doppler derived measurement, 99 % confidence interval was used due to described large variability of inflow/outflow Doppler methodology (Friedmann *et al*. 2008).

Results

The heart rate varied from 124 to 152 beats per minute (bpm), mean 140.6±6.6 bpm. The mechanical AV conduction time interval varied from 92 to 150 ms, mean 122.4±11.5 ms. Mechanical AV conduction time interval (Fig. 2) positively correlated with gestational age ($P<0.001$) and negatively with heart rate ($P<0.001$). There was no correlation between heart rate (HR) and gestational age ($P=0.385$). Normal values (Table 1) in the 20th week of gestation ranged from 94 to 135 ms (mean 113 ms) and in the 26th ranged from 102 to 145 ms (mean 123 ms). Mechanical AV conduction time intervals in the

Table 1. Mechanical PQ intervals (in milliseconds) according to gestational age (in weeks) with 1/99 % confidence intervals, WOG- week of gestation.

WOG	1 %	99 %
16	90	131
17	90	132
18	91	133
19	92	134
20	94	135
21	95	137
22	97	138
23	98	140
24	101	142
25	101	143
26	102	145
27	103	146
28	105	147
29	106	148
30	108	149
31	109	151
32	110	152
33	112	154
34	113	155
35	115	156
36	116	158
37	117	159
38	120	161

20^{th} week of gestation >135 ms and in the 26^{th} week of gestation >145 ms would be suspicious of the presence of the first-degree atrioventricular block. However, mechanical AV conduction time intervals changed not only with gestational age, but also with a different fetal heart rate (Table 2). Using multiple linear regression (Fig. 3), we could estimate predicted AV conduction time intervals including both fetal heart rate and week of gestation in the following regression equation: atrioventricular conduction time = 174.976+(1.315*WOG)-(0.612*HR). Using this formula the predicted mechanical atrioventricular conduction time interval for a given gestational age and heart rate may be calculated. An individual value over the 99 % confidence interval will identify a patient suffering from the first-degree atrioventricular block.

AV conduction time intervals of 21 fetuses with positive maternal SSA/SSB antibodies (Group B) were compared to the reference group (Group A).

Table 2. Mechanical PQ intervals (in milliseconds) according to fetal heart rate (beats per minute) with 1/99 % confidence intervals, WOG- week of gestation.

HR	1 %	99 %	HR	1 %	99 %
100	127	183	141	94	151
101	126	182	142	93	150
102	126	181	143	92	149
103	125	180	144	91	148
104	124	180	145	90	148
105	123	179	146	90	147
106	123	178	147	89	146
107	122	177	148	88	146
108	121	176	149	87	145
109	120	175	150	87	144
110	120	174	151	86	144
111	119	174	152	85	143
112	118	173	153	84	142
113	117	172	154	84	141
114	116	171	155	83	141
115	115	171	156	82	140
116	115	170	157	82	139
117	114	169	158	81	138
118	113	168	159	81	137
119	112	168	160	80	136
120	111	167	161	79	135
121	111	166	162	78	134
122	110	165	163	78	133
123	109	165	164	77	132
124	108	164	165	76	132
125	107	163	166	75	131
126	106	162	167	75	131
127	106	162	168	74	130
128	105	161	169	74	129
129	104	160	170	73	129
130	103	159	171	72	128
131	102	159	172	72	127
132	101	158	173	71	126
133	101	157	174	70	126
134	100	156	175	70	125
135	99	155	176	69	124
136	98	154	177	69	123
137	97	153	178	68	122
138	97	152	179	67	121
139	96	152	180	66	120
140	95	151			

Atrioventricular conduction time intervals did not differ statistically in the 20^{th} or the 26^{th} WOG (P=0.503,

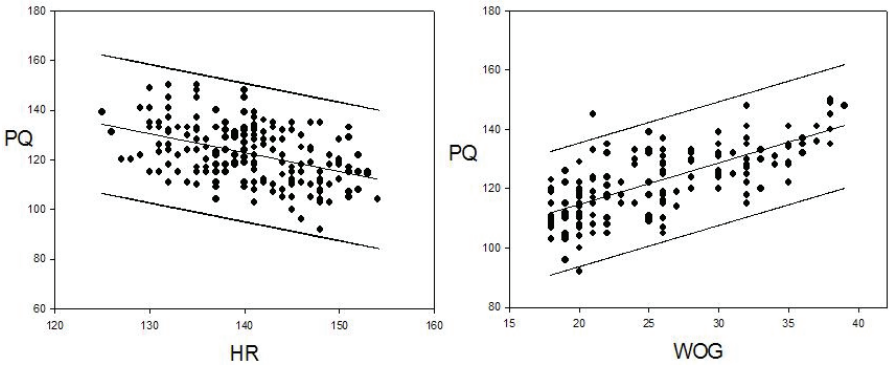

Fig. 2. Left: linear regression of mechanical PQ interval and gestational age (GA). Right: linear regression of mechanical PQ interval and fetal heart rate (HR). Median and 1/99 % confidence intervals are shown.

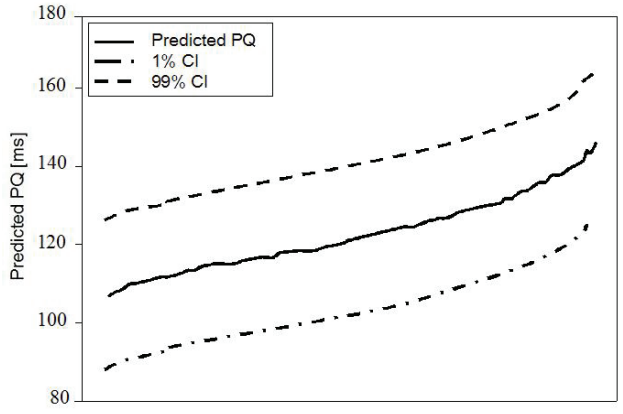

Fig. 3. Prediction of mechanical PQ intervals by multiple linear regression. Median and 1/99 % confidence intervals are shown. An individual value over the 99 % confidence interval would identify a patient suffering from the first-degree atrioventricular block.

respectively 0.614). However, one of 21 fetuses was identified as having prolonged AV conduction time (first-degree AV block) in the 26th WOG (151 ms). Fetus was treated with dexamethasone, did not progress to the second-degree or the third-degree atrioventricular block and AV conduction interval was normal after the birth at the case.

Discussion

Our study showed that the mechanical PQ interval is positively correlated with gestational age and negatively correlated with fetal heart rate reflecting the dependence on sympathetic drive. We did not find any correlation between gestational age and heart rate.

Our results are in accordance with some recently published studies by echocardiography (Friedman *et al*. 2008, Wajakowski *et al*. 2009) or by fetal magnetography (Leuthold *et al*. 1999). However, some other papers suggested that PQ interval is independent on gestational age and fetal heart rate (Bolnick *et al*. 2004).

Atrioventricular block occurs mainly in SSA/SSB-positive pregnancies as the result of maternal antibodies transfer (Brucato *et al.* 2001). However, the concurrent risk factors triggering the immune-mediated inflammation of the atrioventricular nodal and myocardial tissue have not been identified yet. Complete heart block is not reversible by trans-placental treatment and carries a significant risk of death (Schmidt *et al.* 1991, Jaeggi *et al.* 2004). The majority of children born alive with complete AV block require pacemaker before reaching adulthood (Fesslova *et al.* 2009). The administration of corticosteroids to all autoantibody positive pregnancies is not justified because of a potential risk for the mother and the fetus (Saleeb *et al.* 1999, Costedoat-Chalumeau *et al.* 2003). CAVB is a progressive disease (Sonesson *et al.* 2004) and early detection of this process should be the key in the identification of affected fetuses and subsequent prevention of severe forms of the conduction lesion. It has been documented that treatment with fluorinated corticoids may cure the second degree AV block (Saleeb *et al.* 1999). Preventive treatment of fetuses having developed the first-degree AV block would even be a better option. Thus the essence of PQ measurement lies in the early detection of fetuses affected with the first-degree AV block.

Our study suggested reference values for fetuses at various gestational ages. Using normal limits established by this study PQ interval >135 ms in the 20th week and/or >145 ms in the 26th week of gestation can be described as the first-degree AV block. One of the 21 fetuses (9.5 %) from autoimunne-positive pregnancies was identified to have pathologically prolonged AV conduction. The fetus was treated with dexamethasone and did not progress to higher degree of AV block. Thus identification of fetuses with prolonged AV conduction and subsequent treatment may be reasonable and could be of a great importance if applied electively. A different

frequency of the first-degree AV block in fetuses was described (Rosenthal *et al.* 2002, Sonesson *et al.* 2004).

Two Doppler-based methods for fetal assessment of mechanical PQ intervals were described. We used the recording of Doppler signal from the modified 5-chamber view. The other possible method lies on simultaneous acquisition of the superior vena cava and aorta velocities. We considered the second method as more difficult and less practical because of problems with the quality of Doppler signal from the vena cava superior. The question is whether measurement of mechanical PQ interval would be routinely possible in the gynecologist's practice. However, at least fetuses from known maternal antibody positive pregnancies referred to specialized centres could benefit from this Doppler based measurements and benefit from early detected conduction disease based on the described normal limits.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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References

ANDELFINGER G, FOURON JC, SONESSON SE, PROULX F: Reference values for time intervals between atrial and ventricular contractions of the fetal heart measured by two Doppler techniques. *Am J Cardiol* **88**: 1433-1436, 2001.

ASKANASE A, FRIEDMAN D, COPEL J, DISCHE M, DUBIN A, STARC T, KATHOLI MC, BUYON JP: Spectrum and progression of conduction abnormalities in infants born to mothers with anti-SSA/Ro-SSB/La antibodies. *Lupus* **11**: 145-151, 2002.

BOLNICK A, BORGIDA A, EGAN J, ZELOP C: Influence of gestational age fetal heart rate on the mechanical PR interval. *J Matern Fetal Neonatal Med* **15**: 303-305, 2004.

BRUCATO A, FRASSI M, FRANCESCHINI F, CIMAZ R, FADEN D, PISONI MP, MUSCARÀ M, VIGNATI G, STRAMBA-BADIALE M, CATELLI L, LOJACONO A, CAVAZZANA I, GHIRARDELLO A, VESCOVI F, GAMBARI PF, DORIA A, MERONI PL, TINCANI A: Risk of congenital heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. *Arthritis Rhem* **44**: 1832-1835, 2001.

BUYON J, HIEBERT R, COPEL J, CRAFT J, FRIEDMAN D, KATHOLI M, LEE LA, PROVOST TT, REICHLIN M, RIDER L, RUPEL A, SALEEB S, WESTON WL, SKOVRON ML: Autoimunne-associated congenital heart block: demographics, mortality, morbidity an recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* **31**: 1658-1666, 1998.

BUYON J, WALTUCK J, KLEINMAM C, COPEL J: In uteri identification and therapy of congenital heart block. *Lupus* **4**: 116-121, 1995.

CHIA EL, HO TF, RAUFF M, YIP WCL: Cardiac time intervals of normal fetuses using noninvasive fetal electrocardiography. *Prenat Diagn* **25**: 546-552, 2005.

COPEL J, BUYON J, KLEINMAN C: Succesfull in utero therapy of fetal heart block. *Am J Obstet Gynecol* **173**: 1384-1390, 1995.

COSTEDOAT-CHALUMEAU N, AMOURA Z, LE THI HONG D, WECHSLER B, VAUTHIER D, GHILLANI P, PAPO T, FAIN O, MUSSET L, PIETTE JC: Questions about dexamethasone use for the prevention of anti-SSA related congenital heart block. *Ann Rheum Dis* **62**: 1010-1012, 2003.

FESSLOVA V, VIGNATI G, BRUCAO A, DE SANCTIS M, BUTERA G, PISONI MP, CHIAPPA E, ACAIA B, MERONI PL: The impact of treatment of the fetus by maternal therapy on the fetal and postnatal outcomes for fetuses diagnosed with isolated complete atrioventricular block. *Cardio Young* **19:** 282-290, 2009.

FRIEDMAN D, KIM MY, COPEL J, DAVIS C, PHOON C, GLICKSTEN J, BUYON J; PRIDE Investigators: Utility of cardiac monitoring in fetuses at risk for congenital heart block. *Circulation* **117**: 485-493, 2008.

GLICKSTEIN J, BUYON J, FRIEDMAN D: Pulsed Doppler echocardiographic assessment of the fetal PR interval. *Am J Cardiol* **86**: 236-239, 2000.

JAEGGI ET, FOURON JC, SILVERMAN ED, RYAN G, SMALLHORN J, HORNBERGER LK: Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. *Circulation* **110**: 1542-1548, 2004.

LEUTHOLD A, WAKAI R, MARTIN CB: Noninvasive *in utero* assessment of PR and QRS intervals from the fetal magnetocardiogram. *Early Hum Dev* **54**: 235-243, 1999.

ROSENTHAL D, FRIEDMAN DM, BUYON J, DUBIN A: Validation of the Doppler PR interval in the fetus. *J Am Soc Echocardiogr* **15**: 1029-1030, 2002.

SALEEB S, COPEL J, FRIEDMAN D, BUYON J: Comparison of treatment with fluorinated gluccocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the Research Registry for Neonatal Lupus. *Arthiritis Rheum* **42**: 2335-2345, 1999.

SHINOHARA K, MIYAGAWA S, FUJITA T, AONO T, KIDOGUCHI K: Neonatal lupus erythematosus: results of maternal corticosteroid therapy. *Obstet Gynecol* **93**: 952-957, 1999.

SONESSON S-E, SALOMONSSON S, JACOBSON L-A, BREMME K, WAHREN-HERLENIUS M: Signs of first degee heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52-kd antibodies. *Arthiritis Rheum* **50**: 1253-1261, 2004.

SERRA V, BELLVER J, MOULDEN M, REDMAN WG: Computerized analysis of normal fetal heart rate pattern throughout gestation. *Ultrasound Obstet Gynecol* **34**: 74-79, 2009.

SCHMIDT KG, ULMER HE, SILVERMAN NH, KLEINMAN CS, COPEL JA: Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. *J Am Coll Cardiol* **17:** 1360-1366, 1991.

VAN BERGEN AH, CUNEO BF, DAVIS N: Prospective echocardiographic evaluation of atrioventricular conduction in fetuses with maternal Sjögren´s antibodies. *Am J Obstet Gynecol* **191**: 1014-1018, 2004.

WOJAKOWSKI A, IZBIZKY G, CARCANO ME, AIELLO H, MARMANTZ P, OTANO L: Fetal Doppler mechanical PR interval: correlation with fetal heart rate, gestational age and fetal sex. *Ultrasound Obstet Gynecol* **34**: 538-542, 2009.