ORIGINAL RESEARCH PAPER

Natural History of Nonsurgical Complete Atrioventricular Block in Children and Predictors of Pacemaker Implantation

Michal Jičínský, MD,[a] Peter Kubuš, MD, PhD,[a] Markéta Pavlíková, MSc,[b] Miroslav Ložek, MSc,[a,c]
Jan Janoušek, MD, PhD[a]

ABSTRACT

BACKGROUND Data on the natural history of complete atrioventricular block (CAVB) in children are scarce, and criteria for pacemaker (PM) implantation are based on low levels of evidence.

OBJECTIVES This study aimed to evaluate the natural course and predictors of PM implantation in a nationwide cohort of pediatric patients with nonsurgical CAVB.

METHODS All children with CAVB in the absence of structural heart disease presenting from 1977 to 2016 were retrospectively identified, yielding 95 subjects with a mean age of 4.05 years at the first presentation with a follow-up median of 0.80 years (IQR: 0.02-6.82 years). PM implantation was performed according to the available guidelines. Serial 24-hour Holter recordings and echocardiograms were reviewed. Predictors of PM implantation performed >1 month after the first presentation were evaluated.

RESULTS The minimum and mean 24-hour heart rates and maximum RR intervals had a nonlinear correlation with age ($P < 0.0001$ for all). The left ventricular (LV) size was moderately increased, and the shortening fraction was normal in the majority throughout follow-up. PM implantation was performed in 62 patients (65.3%) reaching guideline criteria. The mean 24-hour heart rate at presentation was a predictor of subsequent PM implantation (HR: 0.938; 95% CI: 0.894-0.983; $P = 0.003$ per unit increase) regardless of age at presentation. Patients presenting with a mean 24-hour heart rate >58 beats/min (>75th percentile) had a high probability of freedom from PM within the subsequent 5 years (91.7% vs 44.4%; $P < 0.001$).

CONCLUSIONS Pediatric patients with CAVB showed an age-dependent decrease in heart rate, moderate LV dilation, and preserved LV function. The probability of subsequent PM implantation could be predicted by the heart rate profile at presentation, defining a low-risk group and allowing for individualized follow-up. (J Am Coll Cardiol EP 2023;■:■-■) © 2023 by the American College of Cardiology Foundation.

From the [a]Children's Heart Centre, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; [b]Faculty of Mathematics and Physics, Charles University in Prague, Prague, Czech Republic; and the [c]1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

**ABBREVIATIONS
AND ACRONYMS**

CAVB = complete
atrioventricular block

LV = left ventricular

PM = permanent pacemaker

ROC = receiver-operating
characteristic

Complete nonsurgical atrioventricular block (CAVB) is a rare disease with an incidence of 1 in 15,000 to 20,000 children in the congenital variant.[1,2] Children with untreated CAVB may be affected by a slow heart rate, left ventricular (LV) dilation, and eventual heart failure, all of which may present as fatigue, exercise intolerance, syncope, and even sudden cardiac death.[3-5]
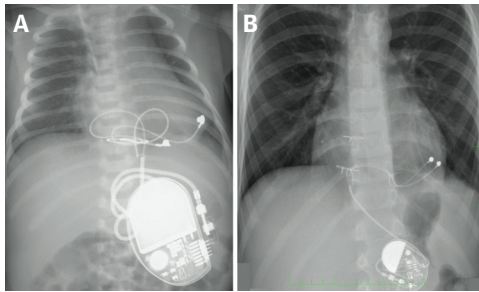
Because there is no currently available causal treatment, the only widely accepted therapy is permanent pacemaker (PM) implantation. However, permanent pacing started in childhood may be associated with future adverse events, including lead failure, infection, and pacing-induced

---

CENTRAL ILLUSTRATION Summary of Natural History of Nonsurgical Complete Atrioventricular Block in Children and Predictive Properties of Mean Heart Rate at Presentation for Future Need of Pacemaker Implantation
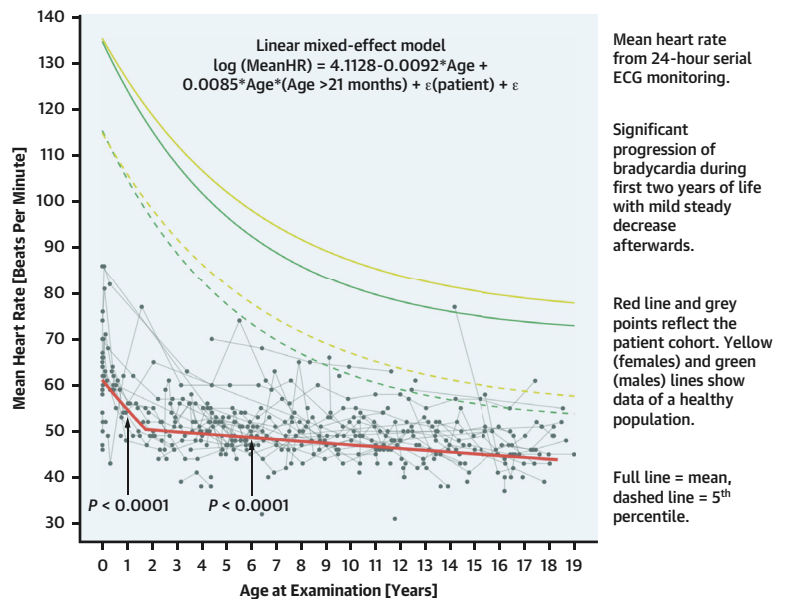
Methods

Nation-wide consecutive patients cohort (N = 95)
Period: 1977-2016
Age: 0 - <19 years at presentation
Follow-up: median 0.8 (IQR 0.02-7.07) years
Analysis of 349 patient-years
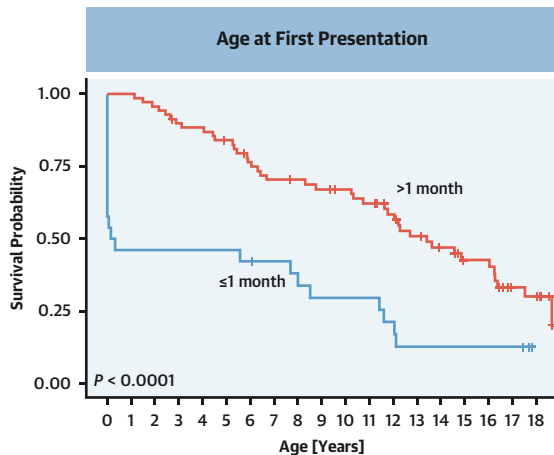Endpoint: pacemaker implantation

Chest X-ray of an epicardial VVI pacemaker in a newborn (A) and an 8-year-old (B).
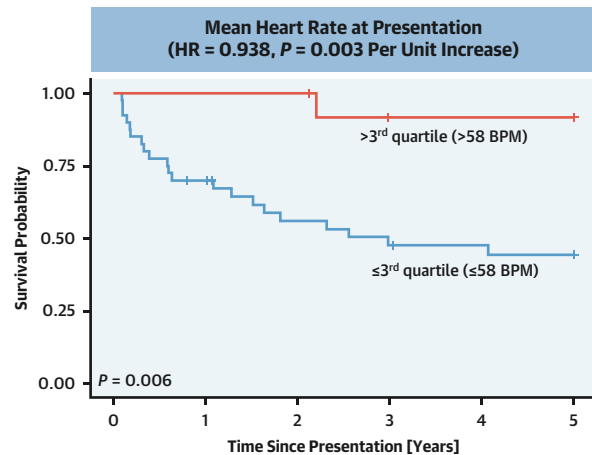
Natural History

Linear mixed-effect model
$\log(\text{MeanHR}) = 4.1128 - 0.0092 \cdot \text{Age} + 0.0085 \cdot \text{Age} \cdot (\text{Age} > 21 \text{ months}) + \varepsilon(\text{patient}) + \varepsilon$

Mean heart rate from 24-hour serial ECG monitoring.

Significant progression of bradycardia during first two years of life with mild steady decrease afterwards.

Red line and grey points reflect the patient cohort. Yellow (females) and green (males) lines show data of a healthy population.

Full line = mean, dashed line = 5th percentile.

Freedom From Pacemaker Implantation

Age at First Presentation

Predictors of Pacemaker Implantation

Mean Heart Rate at Presentation
(HR = 0.938, *P* = 0.003 Per Unit Increase)

Jičínský M, et al. J Am Coll Cardiol EP. 2023;■(■):■-■.

Pediatric patients with nonsurgical complete atrioventricular block show an age-dependent decrease in heart rate, which is most significant in the first 2 years of life. Regardless of age, the mean heart rate at presentation is a strong predictive factor of probability of future pacemaker implantation. ECG = electrocardiography.

cardiomyopathy.[6-9] Thus, pacing should be avoided for as long as safely possible. PM indications for children with nonsurgical CAVB have been repeatedly published as part of both the European and North American guidelines[10,11] but are based on low levels of evidence[1,12-17] because of the absence of larger and randomized studies. We aimed to evaluate the natural course of nonsurgical permanent CAVB in children and to define the predictors of PM implantation (Central Illustration).

METHODS

The clinical database of a single nationwide pediatric cardiovascular center providing PM therapy for all children in the Czech Republic was scanned for pediatric patients diagnosed with a nonsurgical CAVB in the absence of a history of infection, myopathy, metabolic disease, or any but trivial structural heart disease (heamodynamically insignificant arterial duct or patent foramen ovale), yielding a total of 160 patients presenting between 1977 and 2016. Presentation was defined as the first confirmation of CAVB at our center, which occurred thanks to a centralized system of care soon after bradycardia came into medical attention. Cases with transient CAVB or variable degrees of atrioventricular block were excluded, leading to an evaluated cohort of 95 patients. PM therapy was indicated using the international recommendations and guidelines available during the study period.[1,10,11,18-23] The study was approved by the scientific and ethical committee of the Human Physiology and Pathophysiology Board of the Academy of Sciences of the Czech Republic.

DEMOGRAPHICS. The study group consisted of 95 patients, all Caucasian and born in Central Europe; 54 (57%) were female. Age at the first presentation ranged from birth to 18.2 years with a median of 4.05 years (IQR: 0.11-10.30 years). Patients were followed for a median of 0.80 years (IQR: 0.02-6.82 years) until the end of follow-up or PM implantation, providing a total of 349 patient-years for analysis. The end of follow-up was defined as reaching adulthood (before 18 years + 364 days) or death or the last examination before data collection for this study.

LONGITUDINAL DATA ACQUISITION. Longitudinal follow-up data were obtained from the clinical institutional database and patients' files. The following parameters were analyzed:

1. Patients' weight, height, and body mass index compared with values of normal children and adolescents in the Czech Republic as derived from a nationwide anthropological survey[24]

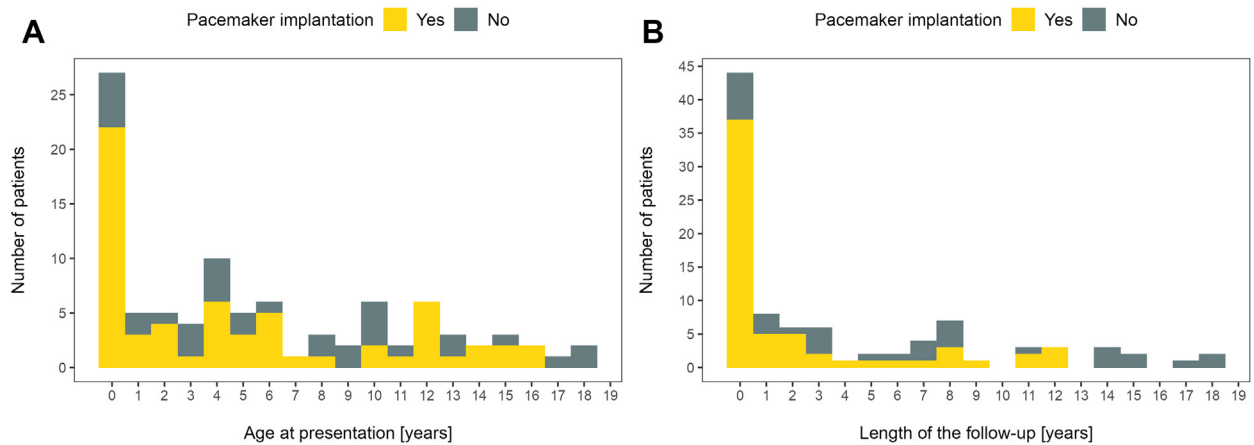**TABLE 1 Cohort Demographics and Characteristics (N = 95)**

Male	41 (43)
Female	54 (57)
Diagnosis in utero	18 (19)
Antibody status known	34 (35.8)
Antibody status positive	27 (28.4)
Antibody status negative	7 (7.4)
Age at presentation, y	4.05 (0.11-10.30)
Age at PM implantation, y	6.19 (1.96-11.97)
Length of follow-up, y	0.80 (0.02-6.82)
24-hour Holter values	
Maximum RR interval at presentation, s	1.70 (1.39-2.18)
Maximum RR interval at PM implantation, s	2.11 (1.78-3.03)
Minimum heart rate at presentation, beats/min	36.0 (31.0-41.8)
Minimum heart rate at PM implantation, beats/min	31.0 (27.0-35.0)
Mean heart rate at presentation, beats/min	52.0 (46.0-57.0)
Mean heart rate at PM implantation, beats/min	46.0 (43.0-49.0)
Echocardiographic values	
LV diastolic diameter z-score at presentation	1.49 (0.27-2.66)
LV diastolic diameter z-score at PM implantation	1.47 (0.58-2.50)
LV shortening fraction at presentation	0.37 (0.31-0.43)
LV shortening fraction at PM implantation	0.39 (0.35-0.43)

Values are n (%) or median (IQR).
LV = left ventricular; PM = permanent pacemaker.

2. Twenty-four-hour Holter recordings were available in 84 of 95 (88.4%) patients at any time before PM implantation with a median of 2.5 recordings (IQR: 1-6 recordings) per patient and missing in 11 of 85 patients who underwent urgent PM implantation because of symptomatic bradycardia. In 76 of 95 (80.0%) patients, 24-hour Holter recordings were available at presentation. All recordings were reviewed to assess the minimum heart rate, the mean 24-hour heart rate, and the maximum RR intervals. The analyzed rhythm was junctional or ventricular escape rhythm in all cases.
3. Echocardiograms were completed in 89 of 95 (93.7%) patients (median: 2.0; IQR: 1-5 per patient) before PM implantation and evaluated to acquire the LV end-diastolic diameter and shortening fraction.
4. Both Holter and echocardiograms were completed before PM implantation in 79 of 95 (83.2%) patients.

Data were expressed as absolute values (heart rate, RR intervals, and LV shortening fraction) and z-scores (LV end-diastolic diameter) based on published normal values.[25]

STATISTICAL ANALYSIS. Data were summarized as the median (IQR) for continuous variables and as absolute and relative frequencies for categoric

FIGURE 1 Age at Presentation and Length of Follow-Up With Relation to Pacemaker Implantation

(A) Patients most frequently presented in the first year of life. Those presenting early required a subsequent pacemaker in the vast majority. **(B)** The majority of patients required pacemaker implantation within 1 year of presentation. See Figure 2 for survival curves of freedom from pacemaker implantation.

variables, respectively. Changes of the minimum heart rate, mean 24-hour heart rate, maximum RR intervals, LV end-diastolic diameter z-score, and LV shortening fraction in function of patients' age were modeled using linear mixed-effect regression models with intrapatient variability as the random factor. Relationships between the LV end-diastolic diameter and the LV shortening fraction and the mean 24-hour heart rate were explored using linear regression. The probability of freedom from PM implantation was evaluated by the log-rank test and subsequently illustrated by Kaplan-Meier curves. Predictors of PM implantation were analyzed in patients with an interval >30 days between the first presentation and PM implantation or the end of follow-up, respectively. The Cox proportional hazards regression model was used with the following independent variables: sex, age at first examination, minimum heart rate, mean 24-hour heart rate, maximum RR intervals, RR ratio (defined as the maximum RR interval divided by the mean RR interval), LV end-diastolic diameter z-score, and LV shortening fraction. The receiver-operating characteristic (ROC) was constructed based on the original data. The value of the mean heart rate at study entry was considered as a "screening test" variable, with possible thresholds ranging from minimum (31.5 beats/min) to maximum (81.5 beats/min) values that appeared in the set. The outcome was survival free from PM implantation between 1 month and 5 years after the initial presentation. Library pROC[26] was used for the ROC curve data calculation. A value of $P \leq 0.05$ was
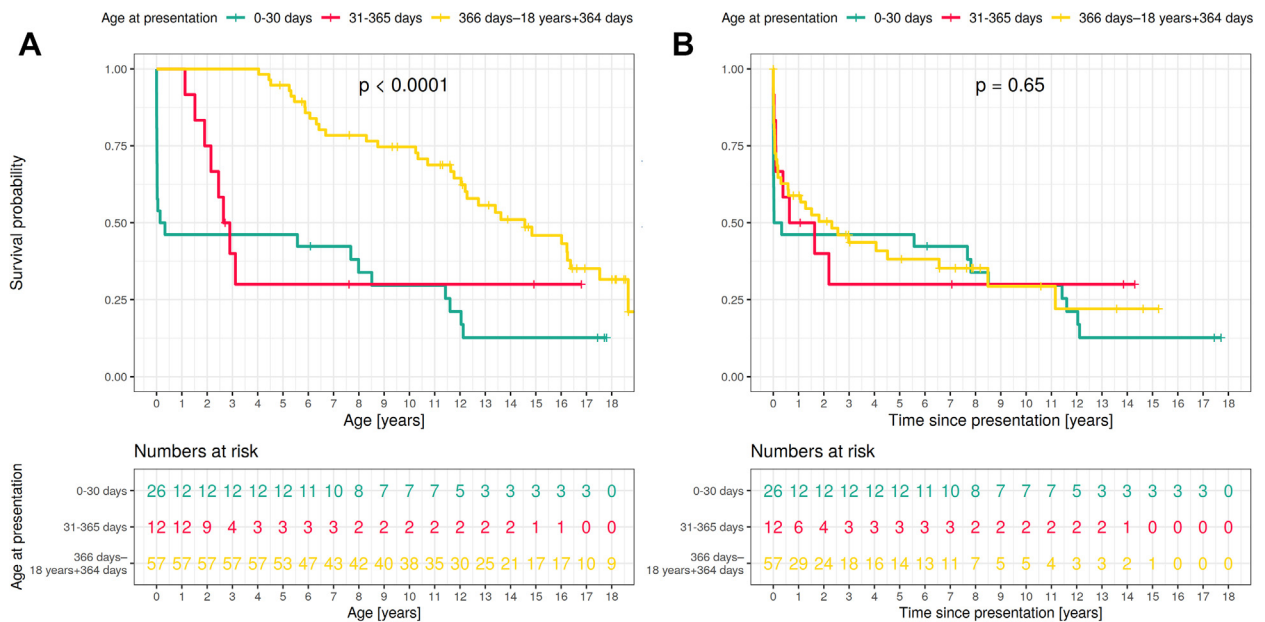
regarded as statistically significant. Statistical language and environment R software (version 4.0.2, R Foundation for Statistical Computing) was used throughout the analysis.

RESULTS

PRESENTATION CHARACTERISTICS. Using age-specific criteria,[27] the QRS complex duration was normal (junctional escape rhythm) in 64 of 95 (67.4%), prolonged (ventricular escape rhythm) in 14 of 95 (14.7 %), and unknown in the remaining 17 of 95 (17.9%) patients at the time of the first presentation. There was no significant difference in the presentation heart rate (24-hour Holter minimum and mean) between patients presenting with junctional or ventricular escape rhythm. No change from junctional

TABLE 2 Indications for PM Implantation

Syncope	3
Exercise intolerance	13
Ventricular dysfunction	16
Heart failure	5
Ventricular rate <55 beats/min in neonates and infants	12
Sudden pauses >2-3× preceding cycle length during ventricular escape rhythm	5
Mean daytime heart rate <50 beats/min	22
Wide QRS complex	14
Complex ventricular ectopy	0

Values are n.

ARTICLE IN PRESS

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. ■, NO. ■, 2023   Jičínský *et al*   **5**
■ 2023:■ - ■   Natural History of Complete Atrioventricular Block

FIGURE 2 Probability of Freedom From Pacemaker Implantation

Patients are divided into 3 groups according to presentation age. **(A)** The probability of freedom from pacemaker implantation according to age. **(B)** The probability of freedom from pacemaker implantation according to the time elapsed since presentation.

escape rhythm to ventricular escape rhythm was observed in any of the patients throughout follow-up. Eighteen (19.0%) patients were diagnosed in utero, and maternal antibody status was known in 34 of 95 patients (35.8%, positive in 27/34) (**Table 1**).
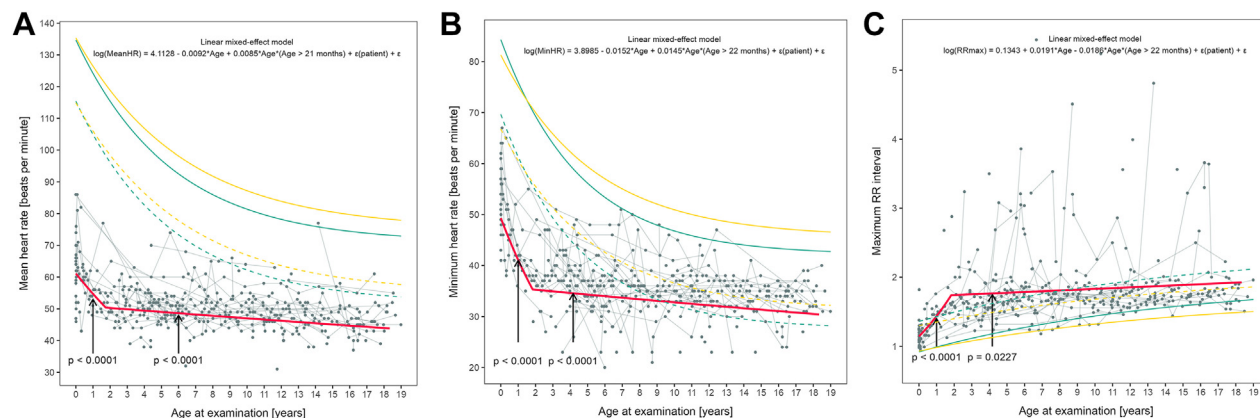
SURVIVAL AND FREEDOM FROM PM IMPLANTATION. None of the patients died during the study period. PM indication criteria were reached in 62 of 95 (65.3%) patients during follow-up (**Figures 1A and 1B**). PM indication was based on the presence of symptoms in 28 of 62 (45.2%) patients or the presence of elective rhythm criteria for PM implantation based on international guidelines and recommendations[1,10,11,18-23] available at the time of indication (34 of 62 patients, 54.8%) (**Table 2**). Only 1 patient experienced syncope before PM implantation during follow-up after the first presentation. The last Holter recording before the syncope revealed a mean 24-hour heart rate below the 25th percentile of the patient group, placing this patient into the high-risk group for subsequent PM implantation as analyzed later.

PM implantation was performed at a median age of 6.19 years (IQR: 1.96-11.96 years); 29 of 62 (46.8%) patients received PM within 1 month after presentation. The overall probability of freedom from PM implantation was 54.1%, 43.0%, 40.3%, 29.6%, and 18.2% at 1, 3, 5, 10, and 18 years after presentation. About 40% of patients presenting as neonates received PM within the first month of life, whereas in patients presenting at >1 year of life, freedom from PM decreased gradually throughout childhood (**Figure 2A**). However, in all age groups, there was a significant number of patients receiving PM early (within 6 months) after presentation (**Figure 2B**).

HEART RATE PROFILE. Absolute values of the mean and minimum 24-hour heart rate and maximum 24-hour RR intervals had a nonlinear correlation with age ($P < 0.0001$ for all) with the maximum progression of bradycardia during the first 2 years of life (**Figures 3A to 3C**). The median value of the mean 24-hour heart rate at presentation was 51.5 beats/min (IQR: 46.0-57.0 beats/min).

LV SIZE AND FUNCTION. The LV end-diastolic diameter showed a significant increase during the first 2 years and then a slower yet also significant decrease until reaching adulthood (**Figure 4A**). There was no change in the LV shortening fraction with age (**Figure 4B**). The majority of patients had preserved LV systolic function (LV shortening fraction ≥0.28)[28] throughout the follow-up with subnormal values being noted at any time in 21 of 89 (23.6%) patients with

FIGURE 3   Heart Rate Profile in Nonsurgical Complete Atrioventricular Block in Children Compared With Healthy Population
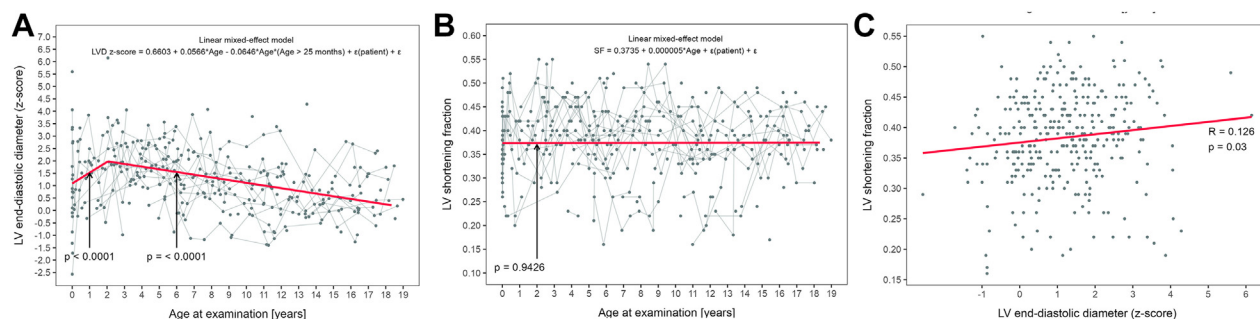

(A) The mean 24-hour heart rate. **(B)** The minimum 24-hour heart rate. **(C)** The maximum 24-hour RR interval. All parameters show a nonlinear correlation with age with a more rapid progression of bradycardia during the first 2 years of life followed by a slower rate profile decline. The **red line** and **gray points** reflect the patient cohort. The **yellow lines** (females) and **green lines** (males) show the data of a healthy population as derived from the study by Salameh et al.[29] **Full line** = mean; **dashed line** = 5th percentile in **A** and **B** and the 95th percentile in **C**.

available data. The LV shortening fraction increased slightly with the degree of LV dilation (**Figure 4C**). None of the patients developed moderate or severe mitral regurgitation during follow-up. The indexed LV end-diastolic dimension showed a significant decrease with an increasing mean 24-hour heart rate regardless of age (**Figure 5**).

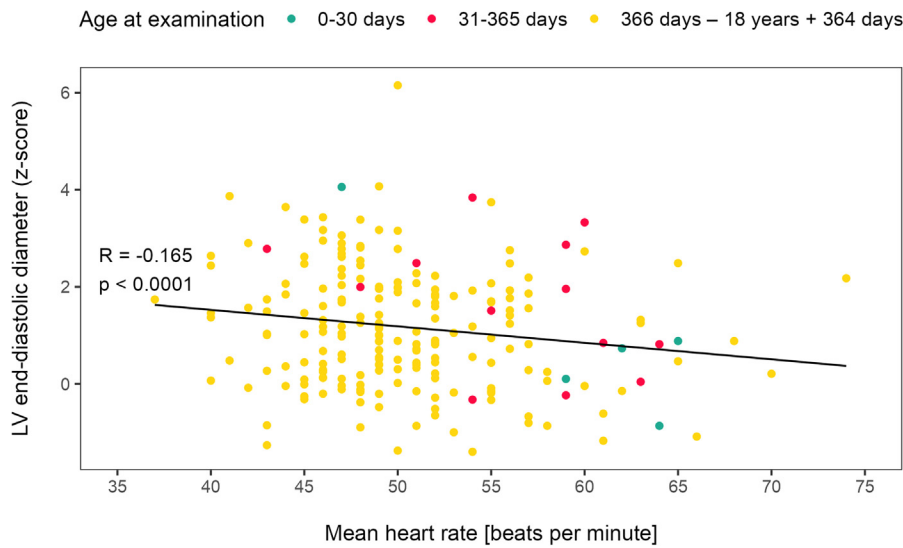**PREDICTORS OF PROBABILITY OF PM IMPLANTATION.** Omitting patients requiring early PM implantation within 30 days after presentation (29 of 95 patients) and patients missing 24-hour heart rate monitoring

data at presentation yielded a group of 53 patients for further evaluation. In these patients, the probability of freedom from PM implantation tended to differ by quartiles of the mean 24-hour heart rate at presentation (median: 53.0 beats/min; IQR: 47.0-58.0 beats/min) regardless of presentation age (**Figure 6A**). The mean 24-hour heart rate at presentation was the only significant univariate predictor of PM implanted >30 days after the first presentation regardless of presentation age with an HR of 0.938 per 1-beat/min increase. Other parameters at presentation such as the minimum heart rate, maximum RR interval, or LV

FIGURE 4   LV Size and Function in Non-surgical Complete Atrioventricular Block in Children
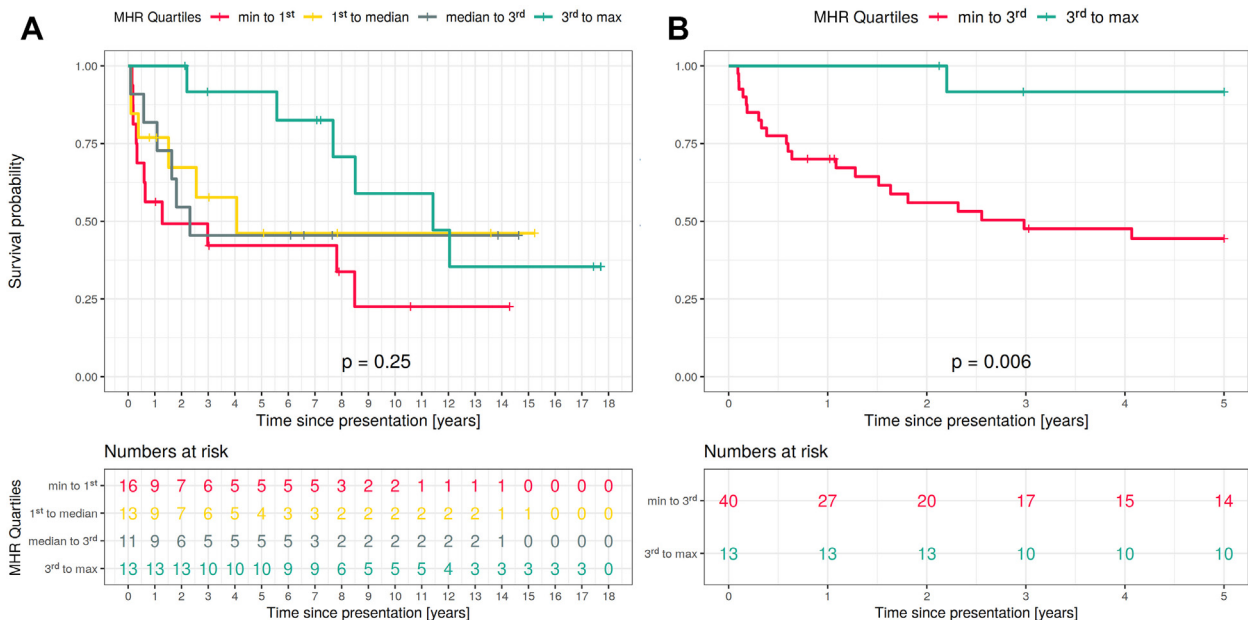

(A) The indexed left ventricular (LV) end-diastolic dimension significantly increased during the first 2 years of life followed by a slower yet significant decrease. **(B)** The LV shortening fraction was stable over time and stayed within normal limits in the majority of patients. **(C)** The LV shortening fraction increased slightly, with the *z*-score of the LV end-diastolic dimension potentially reflecting a Frank-Starling relationship between preload and contractility.

FIGURE 5   **Relationship Between *z* Score of the LV End-Diastolic Dimension and Mean 24-Hour Heart Rate**

A significant increase of the left ventricular (LV) end-diastolic dimension with a decreasing mean 24-hour heart rate (Holter and echocardiography <30 days apart) reflects physiological adaptation to bradycardia.

FIGURE 6   **Influence of Mean Heart Rate at Presentation on the Probability of Freedom From Pacemaker Implantation**

(A) The patient cohort is divided into quartiles of the mean 24-hour heart rate at presentation. Freedom from pacemaker therapy tends to differ by the mean 24-hour heart rate. **(B)** Patients with a mean 24-hour heart rate at presentation in the fourth quartile (>58 beats/min) vs the rest of the group observed for up to 5 years and then censored. A mean 24-hour heart rate >58 beats/min at presentation predicts high freedom from pacemaker implantation within the subsequent 5 years. MHR = mean heart rate.

TABLE 3 Univariate Analysis of Risk Factors for Pacemaker Implanted >30 Days After First Presentation

	HR	95% CI	P Value
Gender (male vs female)	1.328	0.677-2.606	0.412
Age at presentation, y	1.003	0.997-1.009	0.382
Minimum heart rate at presentation, beats/min	0.968	0.934-1.002	0.060
Mean 24-hour heart rate at presentation, beats/min	0.938	0.894-0.983	0.003
Maximum RR interval at presentation	1.406	0.905-2.184	0.149
RR ratio at presentation	2.384	0.947-6.000	0.091
LV end-diastolic diameter z-score at presentation	1.056	0.874-1.277	0.578
LV shortening fraction at presentation	0.674	0.013-35.092	0.845

LV = left ventricular; RR ratio = maximum RR interval divided by mean RR interval.

size and function did not predict PM implantation (Table 3).

Patients presenting with a mean 24-hour heart rate >58 beats/min (>75th percentile) had a significantly higher probability of freedom from PM implantation within the subsequent 5 years compared with the rest of the group (91.7% vs 44.4%; $P = 0.006$; Figure 6B). When used as a screening test, a mean heart rate at presentation >58 beats/min has successfully detected patients who did not need PM implantation between >30 days and 5 years after presentation with a positive predictive value of 92.3% and the area under the ROC curve of 0.75 (Table 4, Figure 7). On the contrary, 95.5% of patients undergoing PM implantation within this interval had a mean heart rate at presentation ≤58 beats/min (specificity).

PHYSICAL DEVELOPMENT OF PATIENTS WITH CAVB. Patients with CAVB did not show significant deviation in growth, weight gain, or body mass index compared with normal national data[24] (Figure 8).
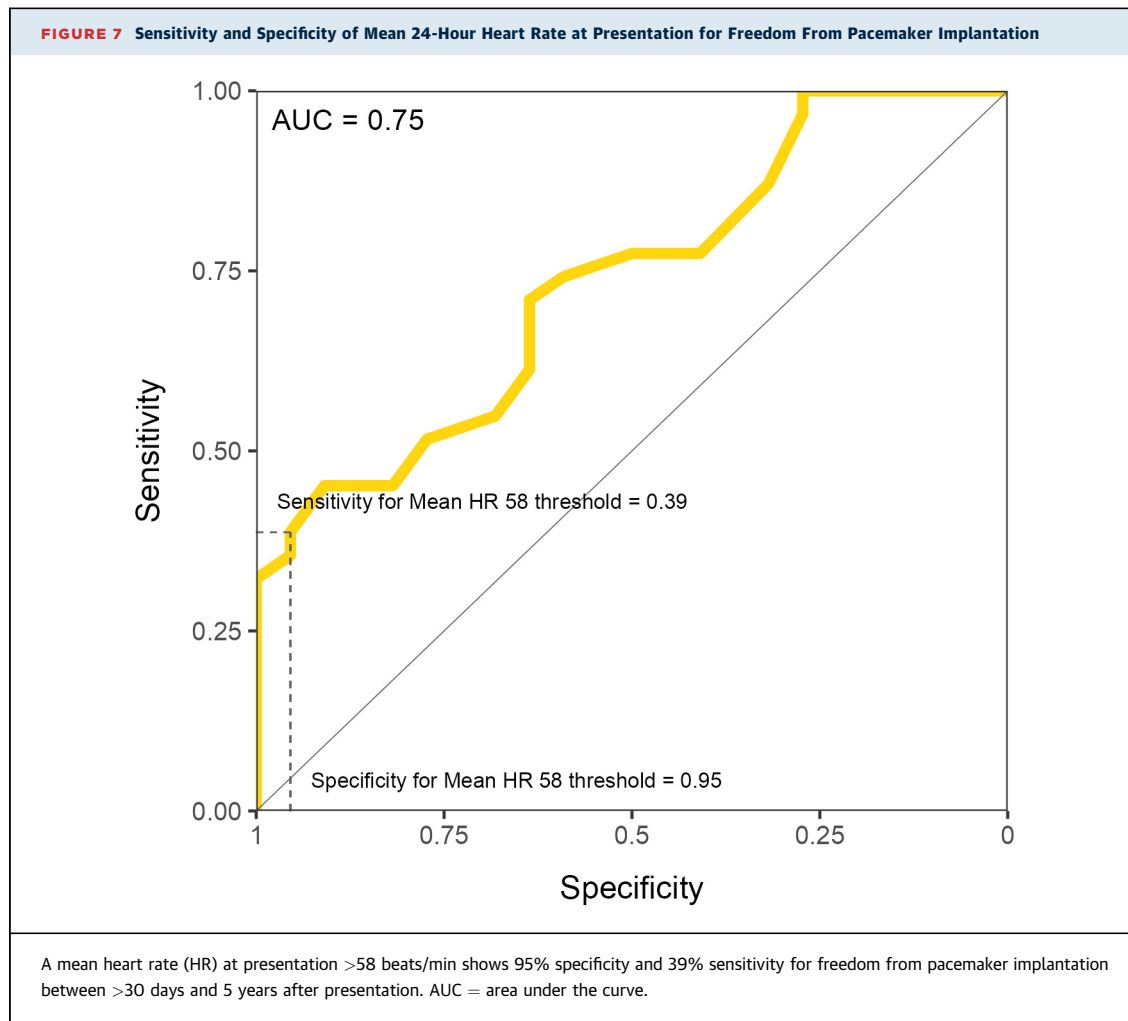
TABLE 4 Sensitivity and Specificity of Mean 24-Hour Heart Rate at Presentation >58 Beats/Min (>75th Percentile) for Freedom From PM Implantation Between >30 Days and 5 Years After Presentation

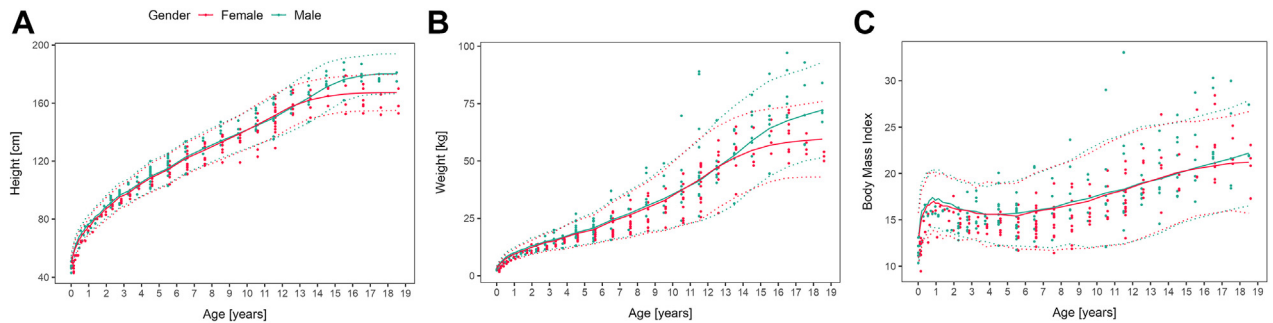|	Definition	N	%
True positive	>58 beats/min, PM−	12	(22.6)
False positive	>58 beats/min, PM+	1	(1.9)
True negative	≤58 beats/min, PM+	21	(39.6)
False negative	≤58 beats/min, PM−	19	(35.9)
Total		53	(100.0)
Sensitivity			(38.71)
Specificity			(95.45)
Positive predictive value			(92.3)
Negative predictive value			(52.5)
Total predictive value			(62.3)

DISCUSSION

This study describes the natural history of patients with nonsurgical CAVB in the era of guideline-driven PM indication and shows that patients with a mean 24-hour heart rate >58 beats/min at presentation were highly likely to be free from PM implantation for the subsequent 5 years. Additionally, the age-dependent heart rate profile, LV metrics, and physical development before eventual PM implantation is presented in the context of normal population values. These detailed data add to the still partially unexplored natural history of nonsurgical CAVB in children. The clinician may be reassured by good tolerance of bradycardia without signs of progressive LV remodeling and normal physical development of children with nonpaced CAVB before reaching PM indication criteria. Our study shows the detailed progression of bradycardia, which is fastest in the first 2 years of life followed by a slow and steady heart rate decrease during the rest of childhood and adolescence. This is in agreement with a previous report by Michaëlsson et al,[3] and heart rate development is similar to the published normal limits for junctional escape rhythm.[19]

Patients in our cohort showed an increasing LV size to compensate for the low heart rate and increasing metabolic demands during the first 2 years of life. The later in life LV size shows a linear decrease, likely reflecting the gradual convergence of the mean 24-hour heart rate in CAVB patients with the mean 24-hour heart rate range of the healthy population,[29] resulting in a decreasing need for cardiac adaptation. The LV systolic function stayed within normal limits in the majority of patients and showed a slight increase with increasing LV size, potentially reflecting a physiologic Frank-Starling relationship between preload and contractility. None of the patients developed dilated cardiomyopathy, which is in agreement with previously published longitudinal echocardiographic data in children with CAVB.[30] Worsening of LV function occurs mainly in the context of PM implantation,[9] and increasing evidence shows the important role of pacemaker-induced cardiomyopathy in the development of LV dysfunction in children with CAVB.[6,31,32] Well-preserved and stable LV function before PM implantation is a proof of good tolerance of bradycardia in young patients with an otherwise normal heart. Thus, progressive LV dilation or worsening of LV function is very unlikely to be an indication for PM implantation.

FIGURE 7 **Sensitivity and Specificity of Mean 24-Hour Heart Rate at Presentation for Freedom From Pacemaker Implantation**

A mean heart rate (HR) at presentation >58 beats/min shows 95% specificity and 39% sensitivity for freedom from pacemaker implantation between >30 days and 5 years after presentation. AUC = area under the curve.

The PM implantation rate in our study agrees with data from Jaeggi et al[13] showing early PM implantation in patients with congenital CAVB presenting in the fetal and neonatal period and a low percentage of freedom from PM implantation while reaching adolescence and adulthood. Several mainly older reports[1,3,13,33] showed that a low heart rate and sudden pauses in ventricular rhythm are likely to be risk factors for syncope and sudden death in young patients with nonsurgical CAVB. Karpawich et al[34] reported that careful evaluation of the ventricular rate at rest may be an effective means of differentiating patients at risk of syncope. Those reports fueled the definition of rhythm-based criteria for elective PM implantation in asymptomatic children. With the availability of PM therapy even for the youngest children, the evaluation of the natural history of nonsurgical CAVB became difficult. Our report is 1 of few currently available studies examining the natural course of CAVB until PM implantation as indicated using the accepted recommendations and guidelines[1,10,11,18-23] available during the study period. It helps to assess the probability of need for PM implantation in the midterm future based on the heart rate profile at the first presentation. The mean heart rate at presentation as obtained from 24-hour Holter recordings of >58 beats/min differentiated a group with a high freedom from PM implantation within the subsequent 5 years with a positive predictive value of 92.3% regardless of age or the respective indication criterion the patients may have reached. This may allow for better patient counseling and individual follow-up including frequency adjustment of serial Holter monitoring. Also, the presented data reassure the safety of the currently used PM implantation guidelines in showing no mortality and a low

FIGURE 8 Physical Development of Patients With Complete Atrioventricular Block Compared With Normal Population

The development of **(A)** height, **(B)** weight, and **(C)** body mass index. The points display individual patients. The **lines** display the mean and 95% confidence limits (±1.96 SD) of the normal population and reflect normal physical development.

incidence of syncope (1/95 patients) in the studied cohort before reaching PM indication, thus indirectly implying high sensitivity to depict patients at risk. However, our study cannot answer the question regarding the false positivity of the PM indication criteria used and whether PM implantation could potentially be deferred without increased risk in a subset of the paced patients.

A recent report by Weinreb et al[35] showed a higher mortality in a pediatric cohort of similar size, which is in contrast to our findings. However, the composite primary endpoint in the study by Weinreb et al[35] was different from ours including death, heart failure, and/or cardiomyopathy and cardiac resynchronization therapy. Thus, as opposed to our study, their patients were followed beyond PM implantation, and only 2 of the 7 deceased patients died before PM therapy was started. Applying similar endpoint criteria as in our report, their mortality rate would be much lower and closer to our outcome.

STUDY LIMITATIONS. This study has several limitations inherent to the character of the studied population. Importantly, the number of patients who underwent PM implantation immediately after presentation did not allow for the evaluation of the natural course of CAVB. On the other hand, a sufficient number of patients were followed for a substantial amount of time (349 patient-years), allowing for a meaningful analysis.

A considerable number of guidelines and recommendations were published and used for the indication of PM implantation during the study period.[1,10,11,18-23] Although some minor changes in guidelines and recommendations have been made over time, they have not had a major influence on the PM indication habits in our cohort.

The study has also not assessed the association of PM technology changes occurring during the study with the likelihood of PM implantation. It cannot be excluded that the burden of PM indication might have decreased over time because of improvements in PM survival as documented in our previously published study.[7]

Maternal antibody status was not known in the majority of the patients. The presence of maternal antibodies is associated with early (fetal or neonatal) presentation of patients with CAVB and early PM implantation,[13] whereas in patients without antibodies, PM implantation could often be deferred until later life.[36] The distribution of age at presentation in our cohort is similar to other studies describing patients with spontaneous CAVB presenting before the age of 15 years.[14] Thus, we may reasonably presume that the percentage of patients with autoimmune CAVB in our cohort may also be similar (ie, around 50%).

Genetic background regarding inherited conduction disorders linked to genetic variants in the ion channel genes SCN5A, SCN1B, SCN10A, TRPM4, and KCNK17 as well as in genes coding for cardiac connexin proteins[37-39] was not evaluated. Therefore, genetic CAVB etiology could not be included as a potential risk factor for PM implantation in the analysis either.

CONCLUSIONS

Pediatric patients with CAVB show an age-dependent decrease in heart rate, a changing degree of LV dilation, and preserved LV function. There is no significant deviation in growth or weight gain. In patients who did not fulfill PM implantation criteria at presentation, the subsequent need for PM implantation may be predicted by the heart rate profile at presentation, defining both the low- and higher-risk groups and enabling an individualized follow-up.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

ADDRESS FOR CORRESPONDENCE: Dr Michal Jičínský, Children's Heart Centre, 2nd Faculty of Medicine, Charles University and Motol University Hospital, V Úvalu 84, 150 06 Prague, Czech Republic. E-mail: michal.jicinsky@fnmotol.cz.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: CAVB is a rare disease requiring PM implantation during childhood in the majority of patients. This report helps the caregiving physicians to better understand the natural history and predict the timing of PM indication, the only available therapy in this population at the moment. It also reassures the normal physical development of the affected children as well as preserved LV function. Such information may also be crucial for patient/parental counseling.

TRANSLATIONAL OUTLOOK: Based on the results of this retrospective single-center study, prospective collaborative research may help confirm the utility of the mean 24-hour heart rate to predict the need and timing of PM implantation. The impact of the different etiologies of CAVB (autoimmune, genetic, and idiopathic) should be assessed to better understand their influence on the natural history. Such data might rationalize long-term patient follow-up strategies before reaching PM indication.

REFERENCES

1. Michaëlsson M, Engle MA. Congenital complete heart block: an international study of the natural history. *Cardiovasc Clin*. 1972;4(3):85-101.

2. Bordachar P, Zachary W, Ploux S, Labrousse L, Haissaguerre M, Thambo J-B. Pathophysiology, clinical course, and management of congenital complete atrioventricular block. *Heart Rhythm*. 2013;10(5):760-766.

3. Michaëlsson M, Riesenfeld T, Jonzon A. Natural history of congenital complete atrioventricular block. *Pacing Clin Electrophysiol*. 1997;20(8):2098-2101.

4. Dewey RC, Capeless MA, Levy AM. Use of ambulatory electrocardiographic monitoring to identify high-risk patients with congenital complete heart block. *N Engl J Med*. 1987;316(14):835-839.

5. Eronen M. Long-term outcome of children with complete heart block diagnosed after the newborn period. *Pediatr Cardiol*. 2001;22(2):133-137.

6. Van Geldorp IE, Delhaas T, Gebauer RA, et al. Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicentre survey. *Heart*. 2011;97(24):2051-2055.

7. Kubuš P, Materna O, Gebauer RA, et al. Permanent epicardial pacing in children: Long-term results and factors modifying outcome. *Europace*. 2012;14(4):509-514.

8. Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. *J Am Coll Cardiol*. 2001;37(1):238-242.

9. Udink ten Cate FE, Breur JMP, Cohen MI, et al. Dilated cardiomyopathy in isolated congenital complete atrioventricular block: early and long-term risk in children. *J Am Coll Cardiol*. 2001;37(4):1129-1134.

10. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;61(3):e6-e75.

11. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;34(29):2281-2329.

12. Michaëlsson M, Jonzon A, Riesenfeld T. Isolated congenital complete atrioventricular block in adult life: a prospective study. *Circulation*. 1995;92(3):442-449.

13. Jaeggi ET, Hamilton RM, Silverman ED, Zamora SA, Hornberger LK. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block: a single institution's experience of 30 years. *J Am Coll Cardiol*. 2002;39(1):130-137.

14. Villain E, Coastedoat-Chalumeau N, Marijon E, Boudjemline Y, Piette JC, Bonnet D. Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status. *J Am Coll Cardiol*. 2006;48(8):1682-1687.

15. Ector H, Rolies L, De Geest H. Dynamic electrocardiography and ventricular pauses of 3 seconds and more: etiology and therapeutic implications. *Pacing Clin Electrophysiol*. 1983;6(3):548-551.

16. Pinsky WW, Gillette PC, Garson A, McNamara DG. Diagnosis, management, and long-term results of patients with congenital complete atrioventricular block. *Pediatrics*. 1982;69(6):728-733.

17. Sholler GF, Walsh EP. Congenital complete heart block in patients without anatomic cardiac defects. *Am Heart J*. 1989;118(6):1193-1198.

18. Frye RL, Collins JJ, DeSanctis RW, et al. Guidelines for permanent cardiac pacemaker implantation, May 1984. A report of the Joint American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Pacemaker Implantation). *Circulation*. 1984;70(2):331A-339A.

19. Garson A. Arrhythmias in pediatric patients. *Med Clin North Am*. 1984;68(5):1171-1210.

20. Gillette PC, Garson A. Diagnosis and management of congenital complete atrioventricular block; pacemakers—indications, implantation and followup. In: Gillette PC, Garson A Jr. eds. *Pediatric Cardiac Dysrhythmias*. Grune & Stratton, Inc; 1981:394-395, 423.A.

21. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: executive summary - a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *J Am Coll Cardiol*. 1998;31(5):1175-1209.

22. Epstein AE, Dimarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report

of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline). *J Am Coll Cardiol*. 2008;51(21):2085–2105.

23. Brugada J, Blom N, Sarquella-Brugada G, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. *Europace*. 2013;15(9):1337–1382.

24. Kobzová J, Vignerová J, Bláha P, Krejcovský L, Riedlová J. The 6th nationwide anthropological survey of children and adolescents in the Czech Republic in 2001. *Cent Eur J Public Health*. 2004;12(3):126–130.

25. Lopez L, Colan S, Stylianou M, et al. Relationship of echocardiographic *Z* scores adjusted for body surface area to age, sex, race, and ethnicity: The Pediatric Heart Network Normal Echocardiogram Database. *Circ Cardiovasc Imaging*. 2017;10(11):e006979. https://doi.org/10.1161/CIRCIMAGING.117.006979

26. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12:77.

27. Park M, Gunteroth W. *How to Read Pediatric ECGs*. 4th ed. Mosby; 2006.

28. Lai WW, Mertens LL, Cohen MS, Geva T. Echocardiography in pediatric and congenital heart disease. In: Lai WW, Mertens LL, Cohen MS, Geva T, eds. *Echocardiography in Pediatric and Congenital Heart Disease From Fetus to Adult*. 2nd ed. John Wiley & Sons, Ltd; 2016:101. https://doi.org/10.1002/9781118742440

29. Salameh A, Gebauer RA, Grollmuss O, Vít P, Reich O, Janoušek J. Normal limits for heart rate as established using 24-hour ambulatory electrocardiography in children and adolescents. *Cardiol Young*. 2008;18(05):467–472.

30. Beaufort-Krol GCM, Schasfoort-Van Leeuwen MJM, Stienstra Y, Bink-Boelkens MTE. Longitudinal echocardiographic follow-up in children with congenital complete atrioventricular block. *Pacing Clin Electrophysiol*. 2007;30(11):1339–1343.

31. Gebauer RA, Tomek V, Kubuš P, et al. Differential effects of the site of permanent epicardial pacing on left ventricular synchrony and function in the young: implications for lead placement. *Europace*. 2009;11(12):1654–1659.

32. Janoušek J, Van Geldorp IE, Krupičková S, et al. Permanent cardiac pacing in children: Choosing the optimal pacing site: a multicenter study. *Circulation*. 2013;127(5):613–623.

33. Molthan ME, Miller RA, Hastreiter AR, Paul MH. Congenital heart block with fatal Adams-Stokes attacks in childhood. *Pediatrics*. 1962;30(1).

34. Karpawich PP, Gillette PC, Garson A, Hesslein PS, Porter CB, McNamara DG. Congenital complete atrioventricular block: Clinical and electrophysiologic predictors of need for pacemaker insertion. *Am J Cardiol*. 1981;48(6):1098–1102.

35. Weinreb SJ, Okunowo O, Griffis H, Vetter V. Incidence of morbidity and mortality in a cohort of congenital complete heart block patients followed over 40 years. *Heart Rhythm*. 2022;19(7):1149–1155.

36. Baruteau AE, Fouchard S, Behaghel A, et al. Characteristics and long-term outcome of non-immune isolated atrioventricular block diagnosed in utero or early childhood: a multicentre study. *Eur Heart J*. 2012;33(5):622–629.

37. Baruteau A-E, Probst V, Abriel H. Inherited progressive cardiac conduction disorders. *Curr Opin Cardiol*. 2015;30(1):33–39.

38. Makita N, Seki A, Sumitomo N, et al. A connexin40 mutation associated with a malignant variant of progressive familial heart block type I. *Circ Arrhythm Electrophysiol*. 2012;5(1):163–172.

39. Schott J, Alshinawi C, Kyndt F, et al. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet*. 1999;23(1):20–21.

IMAGES AND VIGNETTES IN CLINICAL ELECTROPHYSIOLOGY

Multisite Pacing for Heart Failure Associated With Left Ventricular Apical Pacing in Congenital Heart Disease

Karel Koubský, MD, PhD,[a] Jan Kovanda, MD,[a] Miroslav Ložek, MSc,[a,b] Viktor Tomek, MD, PhD,[a] Michal Jičínský, MD,[a] Roman Gebauer, MD,[a] Peter Kubuš, MD, PhD,[a] Jan Janoušek, MD, PhD[a]

L eft ventricular (LV) apical pacing (LVAP) has been shown to preserve LV function in children with complete atrioventricular (AV) block.[1,2] We present 3 pediatric patients (**Figures 1 to 3, Table 1,** Videos 1 to 4) with complex structural heart disease, morphologically left systemic ventricle, and complete AV block, in whom epicardial dual-chamber LVAP was associated with significantly decreased LV systolic function and heart failure symptoms. Coronary artery compression by pre-existing pacing leads was excluded. Upgrade to cardiac resynchronization therapy (CRT) by multisite ventricular pacing directed by echocardiographic speckle tracking analysis led to variable degree of improvement in LV systolic function, reverse LV remodeling, and increase in LV contraction efficiency measured by systolic stretch fraction[3] in 2 of the 3 patients (**Table 1**).

This report demonstrates potential harm associated with LV apical pacing in selected patients with structural heart disease that has not been described previously. Upgrade to multisite CRT pacing should be considered in such cases.
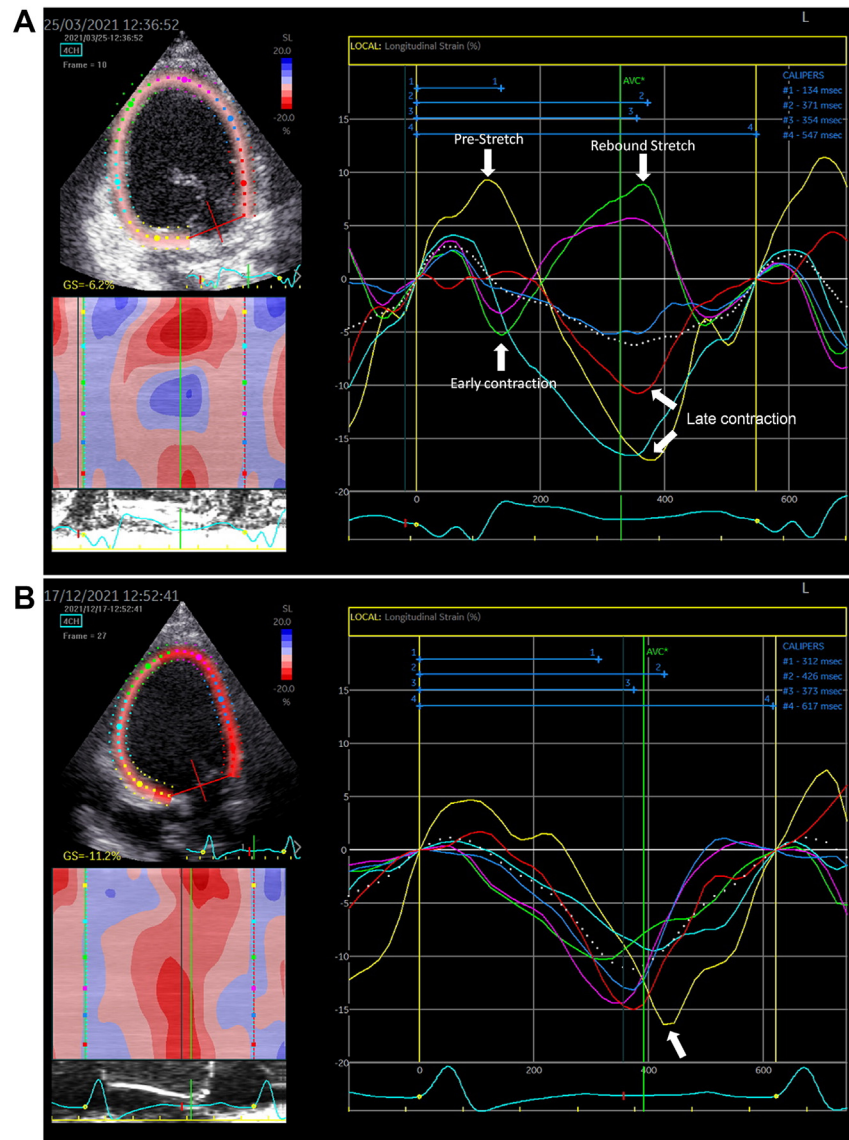
FUNDING SUPPORT AND AUTHOR DISCLOSURES

ADDRESS FOR CORRESPONDENCE: Dr Karel Koubský, Children's Heart Center, University Hospital Motol, V Úvalu 84, 150 06 Prague 5, Czech Republic. E-mail: karel.koubsky@fnmotol.cz.
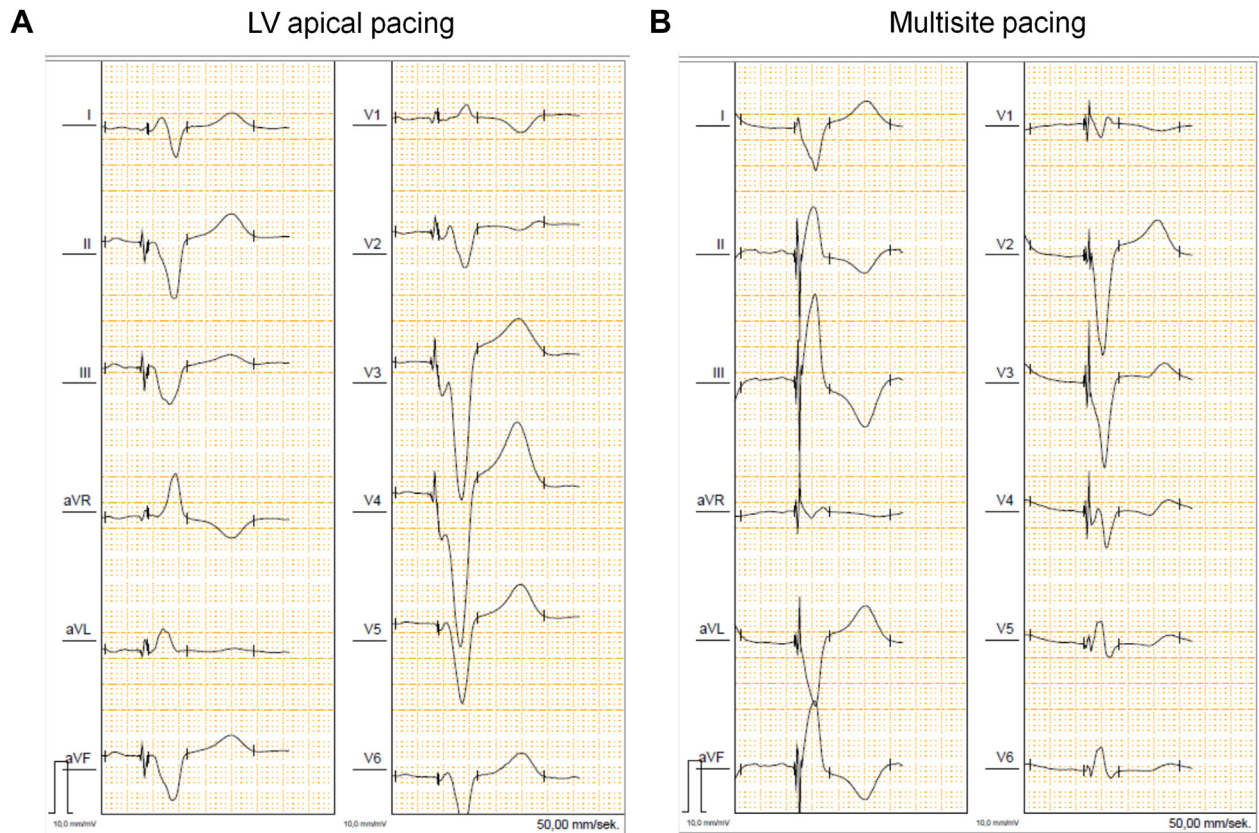
From the [a]Children's Heart Center, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; and the [b]Department of Biomedical Informatics, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.
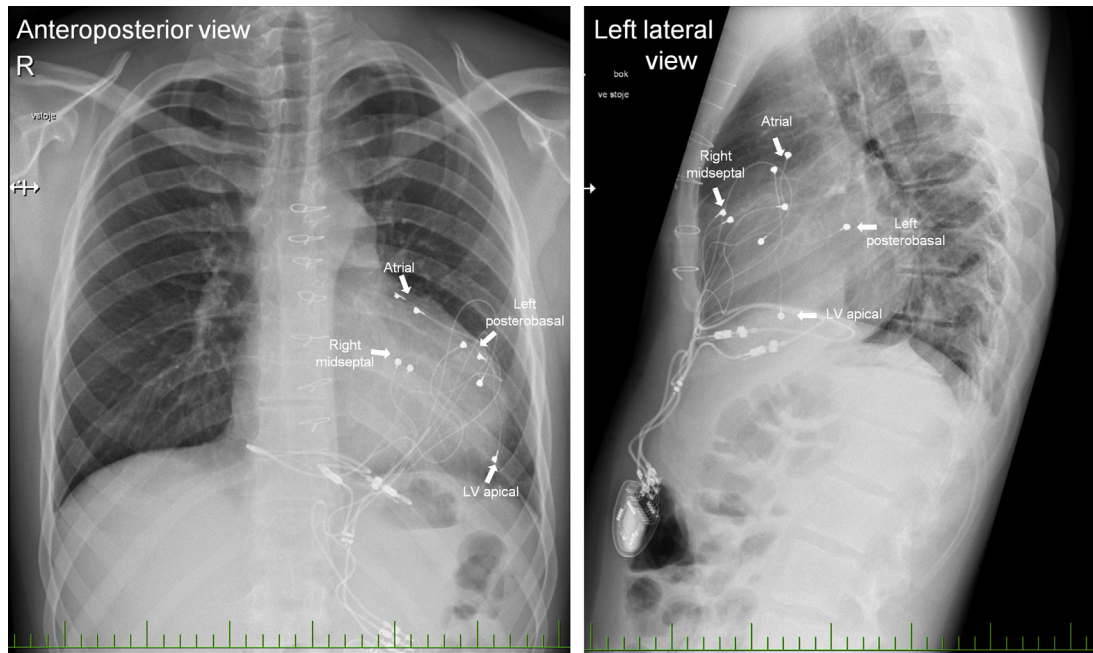
FIGURE 1 LV Mechanical Discoordination

Patient 1 with tricuspid atresia and transposition of great arteries after Fontan type palliation. Age at cardiac resynchronization therapy (CRT) was 5 years. CRT led to clear echocardiographic and clinical improvement. **(A)** Before CRT. Left ventricular (LV) mechanical discoordination: Early apical contraction **(green and cyan curves)**, prestretch and late contraction in the basal septum **(yellow curve)** and free wall **(red curve)** and rebound stretch of the apical segments resembling "classic strain pattern." Peak basal contraction occurs up to 40 ms after aortic valve closure (AVC). The apical-to-basal delay is 237 ms. Such a pattern was not observed in patients with normal LV function.[2] **(B)** After CRT. LV contraction is significantly more synchronous, maximum LV apical-to-basal mechanical delay decreased to 114 ms, and "classic strain pattern" is absent. Peak contraction in the basal septum **(arrow)** is still delayed owing to absence of the midseptal right ventricle outflow tract lead.

FIGURE 2 QRS Morphology

A LV apical pacing   **B** Multisite pacing

Patient 2 with malignant rhabdoid tumor affecting the left ventricle and mitral valve, after tumor resection and mitral valve replacement by mechanical prosthesis, suffering also from plastic bronchitis. Age at CRT was 11 years. CRT led to moderate increase in left ventricular ejection fraction and decrease in left ventricular size along with improvement of left ventricular contraction efficiency. **(A)** During left ventricular apical pacing, QRS duration is 170 ms with superior frontal plane QRS axis. **(B)** After upgrade to multisite pacing, QRS duration decreased to 140 ms and QRS frontal plane axis is inferior. Abbreviations as in **Figure 1**.

FIGURE 3 Lead Positions

Patient 3 with tricuspid stenosis and hypoplastic right ventricle, palliated by a bidirectional cavopulmonary anastomosis resulting in a 1 and 1/2 ventricle circulation. Age at CRT was 17 years. Lead positions after upgrade to multisite pacing along with the original left ventricular apical lead are shown. A biventricular pulse generator with an adapter to bifurcate the LV pacemaker output to the 2 basal leads is used. Despite moderate shortening of the apical-to-basal mechanical delay, there was no significant improvement in LV function or clinical signs of heart failure. We hypothesize that LV dysfunction was so severe that there was little chance of improvement with multisite pacing. Alternatively, effective mechanical resynchronization was not achieved despite proper lead placement and significant QRS duration shortening. This patient was continued on maximum medical heart failure therapy. Indication for heart transplantation will be based on further clinical course. Abbreviations as in **Figure 1**.

TABLE 1 Patient Data and CRT Response

	CRT Response					
	Patient # 1		Patient # 2		Patient # 3	
Age at conventional pacing, yrs	0.4		8.4		10.8	
Age at CRT, yrs	5.3		11.6		17.8	
Follow-up after CRT, mo	8.9		3.9		5.3	
Pacing sites	LVA, LVPW		LVA, LVPW, MRVOT		LVA, LVPW, MRVOT	
	Before	**After**	**Before**	**After**	**Before**	**After**
NYHA functional class	2	1	2	2	2	2
NTproBNP, ng/L	610	253	N/A	191	2,906	7,497
QRS duration, ms	130	110	170	140	180	120
LVEDVi, ml/sqm BSA	141	97	68	58	164	148
LVESVi, ml/sqm BSA	101	47	38	27	125	109
LVEF, %	29	51	44	55	24	26
LV index of myocardial performance	1.15	0.42	0.35	0.13	0.77	0.51
LV apical to basal delay, ms	237	114	123	42	364	209
Aortic valve closure to latest peak basal LV strain, ms	40	39	85	12	47	82
LV systolic stretch fraction	0.36	0.33	0.70	0.24	0.42	0.32
Early LV apical contraction + LV basal pre-stretch	1	0	1	0	1	0
Late LV basal contraction + LV apical rebound stretch	1	0	0	0	1	1

BSA = body surface area; CRT = cardiac resynchronization therapy; EF = ejection fraction; LV = left ventricle; LVA = left ventricular apex; LVEDVi = indexed left ventricular end-diastolic volume; LVESVi = indexed left ventricular end-systolic volume; LVPW = left ventricular posterior basal wall; MRVOT = midseptal right ventricular outflow tract; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

REFERENCES

1. Janoušek J, van Geldorp IE, Krupickova S, et al. Permanent cardiac pacing in children: choosing the optimal pacing site: a multicenter study. *Circulation*. 2013;127:613–623.

2. Kovanda J, Ložek M, Ono S, Kubuš P, Tomek V, Janoušek J. Left ventricular apical pacing in children: feasibility and long-term effect on ventricular function. *Europace*. 2020;22(2):306–313.

3. Russell K, Eriksen M, Aaberge L, et al. Assessment of wasted myocardial work: a novel method to quantify energy loss due to uncoordinated left ventricular contractions. *Am J Physiol Circ Physiol*. 2013;305:H996–1003.

APPENDIX For supplemental videos, please see the online version of this paper.

Prenatální diagnostika kardiálního postižení u lupus neonatorum

Tomek V., Gilík J., Kovanda J., Fiala K., Jičínský M.

Dětské kardiocentrum 2. LF UK a FN Motol, Praha, přednosta prof. MUDr. Jan Janoušek, Ph.D.

SOUHRN

Transplacentární přenos mateřských autoprotilátek anti-Ro a anti-La může vést k onemocnění srdce zahrnující atrioventrikulární blokádu a kardiomyopatii. Kompletní atrioventrikulární blokáda plodu je závažným projevem kardiálního postižení u lupus neonatorum, které může vést k rozvoji srdečního selhání a až k intrauterinnímu úmrtí plodu. Diagnostika atrioventrikulární blokády 1. až 3. stupně je pomocí ultrazvukového vyšetření poměrně snadná. Možnosti terapeutického ovlivnění kompletní atrioventrikulární blokády jsou v prenatálním období dosud výrazně limitované. Konverze úplné formy atrioventrikulární blokády na sinusový rytmus není možná. Léčba plodů s již vzniklou kompletní blokádou pomocí glukokortikoidů (dexamethason) nepřináší prokazatelný pozitivní efekt pro plod ani pro novorozence. Nejlepší možností zábrany vzniku atrioventrikulární blokády je preventivní léčba vyžadující sledování a správnou stratifikaci vysoce rizikové skupiny těhotných, zřejmě dle přítomnosti a výše titru anti-Ro52 kDa. Atrioventrikulární blokádu 1. stupně lze stanovit echokardiografickým měřením plodů rizikových těhotných. K rozvoji atrioventrikulární blokády ale může dojít velmi rychle, a to i v průběhu několika hodin. Preventivní podání glukokortikoidů s transplacentárním přenosem může zabránit rozvoji kompletní formy, často v kombinaci s imunoglobuliny. Hydroxychlorochin je slibným lékem v prevenci kardiálního postižení u lupus neonatorum..

KLÍČOVÁ SLOVA

prenatální diagnóza – echokardiografie – plod – lupus neonatorum – atrioventrikulární blok

SUMMARY

**Tomek V, Gilík J, Kovanda J, Fiala K, Jičínský M.
Prenatal diagnosis of cardiac manifestation associated with lupus neonatorum?**
Transplacentar transfer of maternal anti-Ro and/or anti-La autoantibodies may result in cardiac disease such as heart block and cardiomyopathy. Complete congenital heart block is a rare but devastating condition of cardiac Neonatal Lupus and may result in heart failure and foetal death. Complete atrioventricular block is considered to be irreversible. It seems that maternal anti-Ro levels ant presence of anti-Ro52 component predict fetuses at high risk of immune-mediated cardiac complications. Maternally administered corticosteroids may limit the progression of the 1st or the 2nd atrioventricular block. However, the transition from normal sinus rhythm to the third-degree atrioventricular rhythm may be rapid (< 24 hours). Dexamethasone given during pregnancy may achieve normalization of prolonged atrioventricular conduction time interval and averts the progression to complete heart block, often used in combination with intravenous immunoglobulin administration. In fetuses with complete AV block, the effect of steroid treatment on outcome is not proven. Hydroxychloroquine treatment during preganancy has been asscotiated with a decreased recurrence of cardiac Neonatal Lupus.
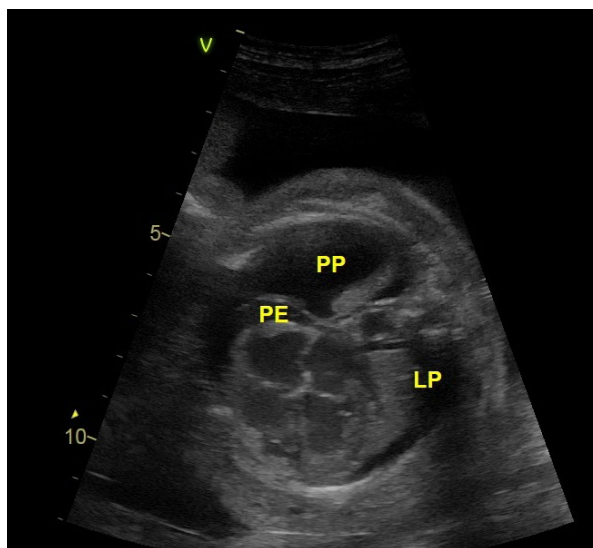
KEY WORDS

prenatal diagnosis – echocardiography – fetus – neonatal lupus – atrioventricular block

ÚVOD

Transplacentární přenos mateřských autoprotilátek anti-Ro a anti-La může vést k onemocnění srdce zahrnující atrioventrikulární (AV) blokádu a kardiomyopatii. Kompletní AV blokáda (AVB) plodu je závažným projevem kardiálního postižení u lupus neonatorum, které může vést k rozvoji srdečního selhání a až k intrauterinním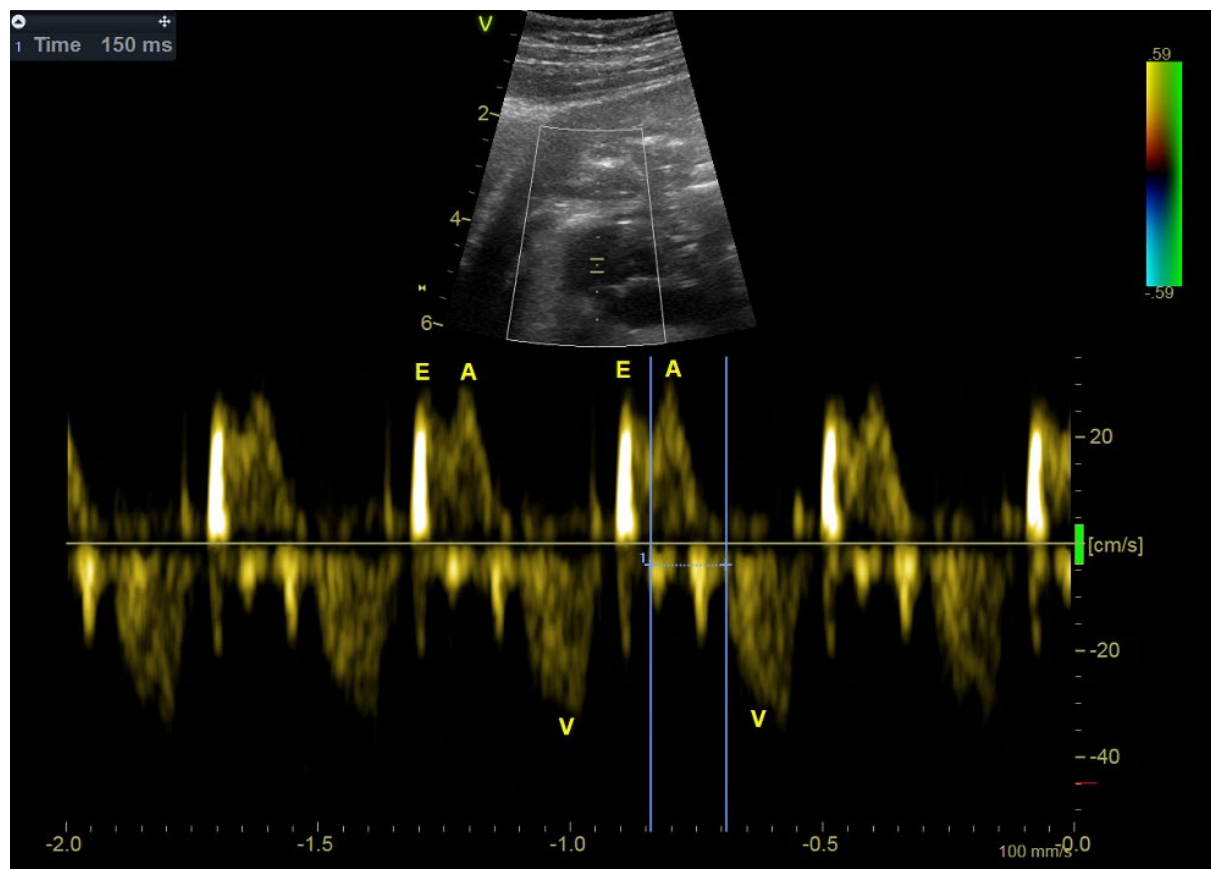u úmrtí plodu (1). Anti-Ro a anti-La jsou autoprotilátky proti extrahovaným nukleárním antigenům a jsou přítomné u pacientů se systémovým onemocněním (systémový lupus erythematodes – SLE, Sjögrenův syndrom a další). Tyto mateřské protilátky přestupují placentou do oběhu plodu a vyvolávají zánět v oblasti AV uzlu vedoucí k postupnému vývoji AV blokády. K té dochází typicky mezi 20. až 24. gestačním týdnem. O proběhlém zánětu v oblasti AV uzlu svědčí fibrotická přestavba uzlu u kongenitálního AVB 3. stupně (2). V kombinaci s hydropsem a níz-

Obr. 1 Rozsáhlý hydrops u plodu s kompletní formou atrioventrikulární blokády ve 26. gestačním týdnu při tepové frekvenci 54/min
PP – pravá pleura, LP – levá pleura, P – perikard

kou komorovou frekvencí (pod 55/min) představuje vysoké riziko intrauterinního úmrtí nebo předčasného porodu (3). Ve zvláště nepříznivých případech může dojít až k progresi autoimunitně navozeného zánětu v endokardiální fibroelastózu (4, 5) a dilatační kardiomyopatii (6). Kompletní AVB se vyskytuje v 1–2 % plodů matek se séropozitivou anti-Ro, anti-La, což odpovídá incidenci 1/15 000 až 1/20 000 živě narozených dětí (7). Rizikem pro možný vývoj lupus neonatorum u plodu není jen samotná přítomnost autoprotilátek v krvi matky, ale vysoký titr anti-Ro autoprotilátek (8). Autoprotilátky anti-Ro 52 kDa mají (na rozdíl od anti-Ro 60 kDa) dominantní roli při vzniku AV blokády (9, 10).

Kompletní atrioventrikulární (AV) blokáda vede k bradykardii plodu. Srdeční frekvence při kompletní formě blokády se pohybují od 45 do 70/min. Lidský plod toleruje nízké srdeční frekvence lépe než vyšší, ale i tak může vést k srdečnímu selhání (obr. 1). Kumulativní neonatální a prenatální úmrtnost se udává mezi 10–30 % u plodů s AV blokádou (3). Hlavními rizikovými faktory úmrtí jsou: hyd-

Obr. 2 Atrioventrikulární blokáda 1. stupně. Pulzní dopplerovské vyšetření simultánně registruje vtok a výtok z levé komory, prokazuje prodloužený mechanický atrioventrikulární interval 150 msec mezi kontrakcí síně (A) a kontrakcí komory (V).
E – fáze rychlého plnění komory

rops plodu, snížená funkce levé komory a nízké gestační stáří plodu v okamžiku diagnózy (3, 11, 12).

DIAGNOSTIKA ATRIOVENTRIKULÁRNÍ BLOKÁDY

Atrioventrikulární blokáda se vyznačuje bradykardií plodu a vzniká na základě poruchy vedení vzruchu. Ta může být způsobena buď změněnou funkcí iontových kanálů, nebo snížením počtu buněk převodního systému na podkladě fibrotizace a degenerativních změn. K poruše vedení vzruchů může dojít na úrovni atrioventrikulárního uzlu (suprahisálně), v oblasti Hisova svazku (intrahisálně) nebo infrahisálně až ve větvení na Purkyňova vlákna. Dle míry zachování AV převodu rozlišujeme tři stupně AV blokády (AVB):
• 1. stupeň se zachovalým převodem poměrem převodu mezi síněmi a komorami 1 : 1, ale s prodloužením AV převodu (obr. 2)
• 2. stupeň, kdy některé síňové kontrakce nejsou převedeny na komory. Rozlišujeme dva typy AVB 2. stupně:

◦ Wenckebachův typ, při kterém dochází k postupnému prodlužování PQ intervalu vedoucího až k výpadu AV převodu
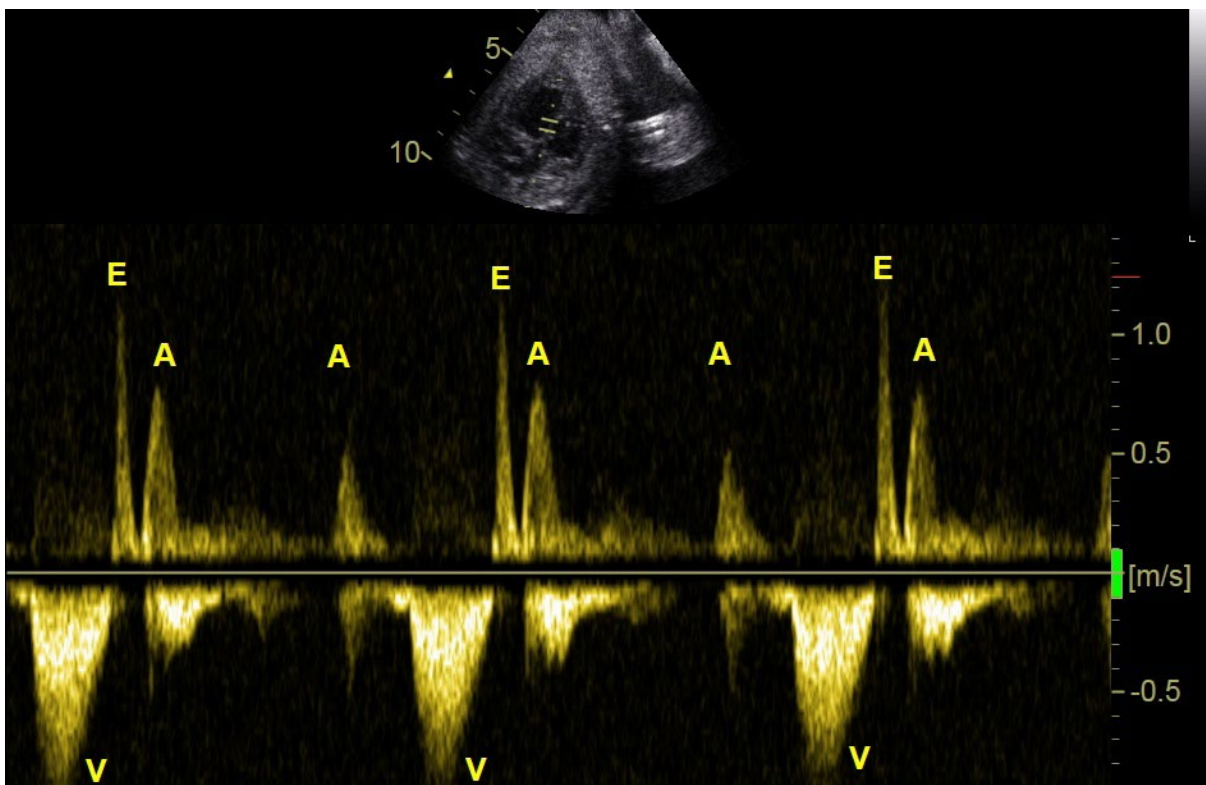◦ Mobitz II, kdy je výpadek převodu ze síní na komory náhlý (obr. 3, 4)
• 3. stupeň je rovněž nazýván jako kompletní AV blokáda a je definován jako úplná disociace akce síní a komor. Výsledná tepová frekvence plodu je dána pouze frekvencí komor.

Diagnostika AV bloku spočívá v echokardiografickém vyšetření. Již ve 2D obraze je patrná pomalá frekvence komor při normálním sinusovém rytmu síní. Diagnózu lze ověřit dopplerovským vyšetřením nebo M-způsobem, kdy je možné simultánně registrovat kontrakci síní a komor (obr. 5).
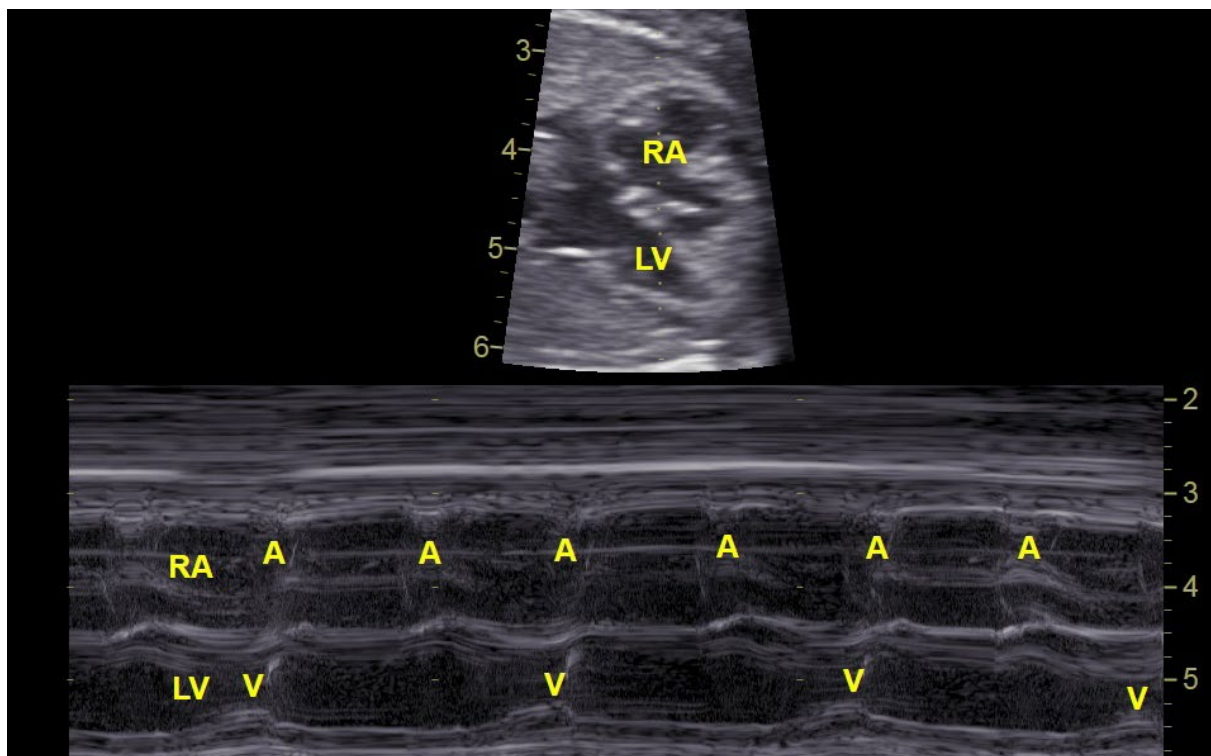
MOŽNOSTI LÉČBY KARDIÁLNÍHO POSTIŽENÍ LUPUS NEONATORUM U PLODU
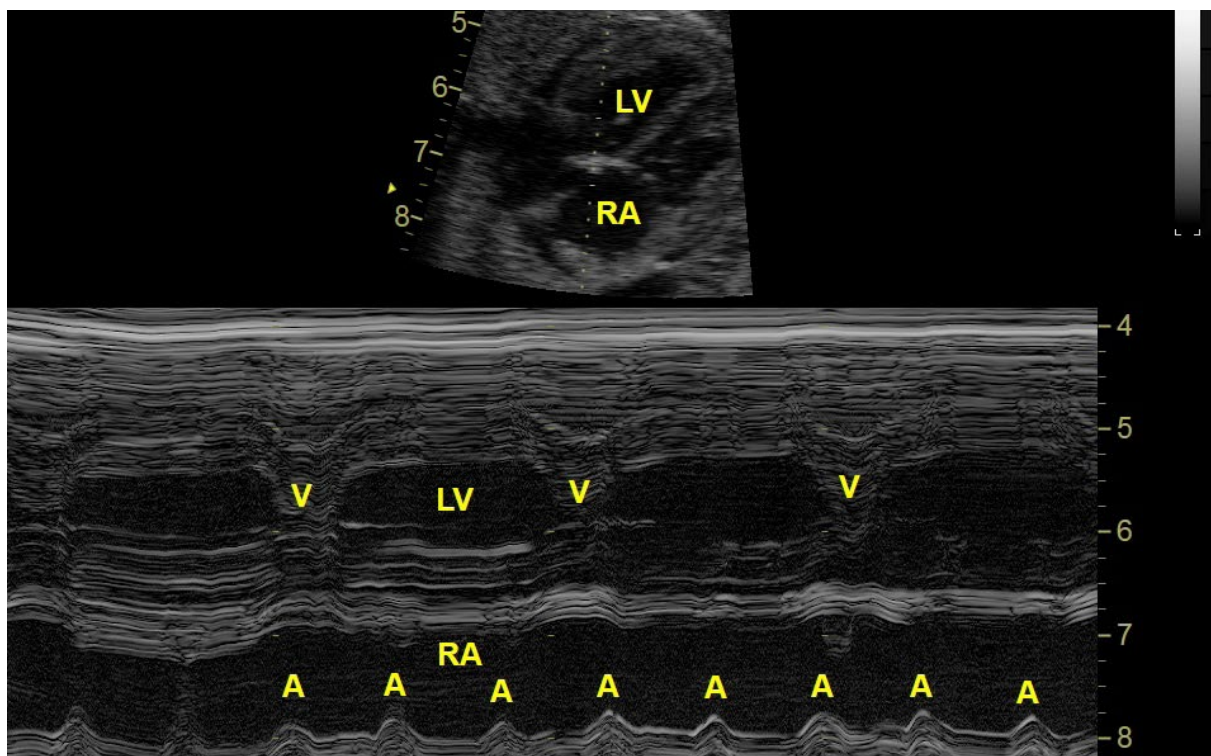
Elektrická stimulace srdce
V postnatální léčbě AV blokády dominuje nefarmakologický přístup – elektrická stimulace

Obr. 3   Atrioventrikulární blokáda 2. stupně typu Mobitz II. Na komory (V) se převádí pouze každý druhý stah síní (A); pulzní dopplerovské vyšetření při simultánním zobrazení vtoku a výtoku levé komory
E – fáze rychlého plnění komory

Obr. 4 Atrioventrikulární blokáda 2. stupně typu Mobitz II zachycena pomocí Mmode. Na komory (V) se převádí pouze každý druhý stah síní (A).
RA – pravá síň, LV – levá komora

Obr. 5 Kompletní atrioventrikulární blokáda u plodu registrovaná na úrovni levé komory (LV) a pravé síně (RA), echokardiografie M-způsob zobrazení detekující kontrakci síní (A) a komor (V). Pravidelný sinusový rytmus o frekvenci 120 tepů/min není převáděn na komory, které mají svoji vlastní aktivitu 62 tepů/min.

srdce. Její princip spočívá v tvorbě nadprahových elektrických impulzů vedoucích k opakovanému dráždění (stimulaci) myokardu, odkud se srdeční vzruch šíří na ostatní tkáň. Trvalá kardiostimulace je v dnešní době vyzkoušenou a plně funkční metodou, která při správném nastavení stimulačního režimu a správně zvoleném umístění stimulačních elektrod umožňuje téměř fyziologickou aktivaci srdečního svalu. Nastavení kardiostimulátoru zabezpečí nejen správnou sekvenci aktivace síní a komor, ale zachová i vhodné synchronní šíření impulzu v obou komorách, včetně možnosti tzv. biventrikulární stimulace (stimulace obou komor s nastavitelným interventrikulárním intervalem). Moderní stimulační systém dokáže adekvátně frekvenčně reagovat na metabolické změny organizmu i pomocí metabolických senzorů (mechanické vibrace při fyzické zátěži, změně pH či saturace kyslíku v centrální žíle, tlaku v pravé komoře, délce repolarizace a řadě dalších parametrů) a zabezpečit srdeční výdej dle potřeb organizmu.

Prenatálně je elektrická stimulace srdce nemožná. Nutnost implantace stimulačních elektrod (intravaskulárně nebo epikardiálně) s použitím pacemakeru, by teoreticky byla optimální léčebnou metodou, ale je v současné době technicky nepředstavitelná. Jedinou možností je tedy pokus o **farmakologické ovlivnění této závažné bradyarytmie.**

Glukokortikoidy
Teoretický podklad léčby spočívá jednak v zabránění probíhajícího zánětu a fibrotizace atrioventrikulárního uzlu při prokázaném přenosu autoprotilátek od matky a zvýšení tepové frekvence plodu tak, aby se zlepšil srdeční výdej (13, 14). Podání fluoridovaných glukokortikoidů (dexamethason v dávce 4–8 mg/den) může zabránit progresi v AV blokádu 3. stupně, která je považována za ireverzibilní poškození. Byla prokázána úspěšná konverze AV blokády 2. stupně na sinusový rytmus (15). Konverze úplné AV blokády na sinusový rytmus nebyla prokazatelně dokumentována. Smysl aplikace glukokortikoidů (dexamethason 2–4 mg/den) při již kompletní AV blokádě byl spatřován v imunomodulačním efektu steroidní léčby a zabránění rozvoje autoimunitního zánětu myokardu a jeho další progresi v dilatační kardiomyopatii (14). Léčba glukokortikoidy ale musí být jasně indikována pro řadu nepříznivých důsledků pro plod, zejména pro vývoj mozku (16, 17). Předpoklad efektu transplacentární steroidní léčby se opíral především o práci Jaeggiho (18), který popsal pozitivní vliv dexamethasonu na osud plodu. Problémem této studie je však srovnání dvou rozdílných časových období – staršího

bez kortikoterapie a mladšího s plody léčenými steroidy. Lze oprávněně namítnout, že mortalita novorozenců byla ovlivněna obecným zlepšením kvality péče a znevýhodnila historicky starší neléčené plody. V rámci multicentrické retrospektivní studie jsme neprokázali žádný rozdíl mezi léčenou a neléčenou skupinou plodů s již vzniklou kompletní AV blokádou (12). Naopak, těhotenství u léčených plodů bylo častěji ukončeno porodem sekcí a plody měly i nižší hmotnost, zřejmě v důsledku nižšího gestačního stáří. Ze sledovaných 175 plodů intrauterinně zemřelo deset a dalších 12 postnatálně (celková úmrtnost 13 %). Hlavním rizikovým faktorem mortality bylo gestační stáří plodu < 20 týdnů, frekvence komor < 50 tepů/min a snížená funkce levé komory. Při znalosti nežádoucích účinků glukokortikoidů na lidský plod, jejich neefektivní podávání při již vzniklé ireverzibilní AV blokádě, by mělo být podávání kortikoidů limitováno pouze na případy AV blokády 1. a 2. stupně.

Betamimetika
Osud těhotenství by mohlo zlepšit při poklesu srdeční frekvence podání β-sympatomimetik – terbutalinu nebo salbutamolu (13). Jejich použití pro zvýšení tepové frekvence plodu má opodstatnění ve zjištění, že nízké tepové frekvence < 55/min jsou spojeny s vysokým rizikem kardiální dekompenzace při nízkém srdečním výdeji. Jejich pozitivní efekt byl opakovaně prokázán. Ani tato léčba ale nedokáže vždy zajistit úpravu či prevenci srdečního selhání. Navíc často dochází po iniciálním zvýšení tepové frekvence k jeho opakovanému poklesu. Betamimetika mohou být v těhotenství špatně tolerována a výskyt palpitací, anxiozity či bolestí hlavy je častý.

Imunoabsorpce
Další možnou léčbou je extrakorporální imunoadsorpce. Cílem je selektivní odstranění imunoglobulinů G. Tato metoda byla úspěšně využita dosud jen na malých souborech a při kombinované léčbě (19). Její efekt je navíc pouze dočasný, při již vzniklé kompletní blokádě její benefit prokázán nebyl. Větší soubory efekt v zábraně vzniku kompletní AV blokády nijak neprokázaly (20).

Imunoglobuliny
Ani podávání imunoglobulinů matce nemá jednoznačně pozitivní efekt na osud plodů postižených neonatálním lupusem (21, 22). Role imunoglobulinů byla u plodu prokázána v ovlivnění kardiomyopatie, resp. „karditidy", na obdobném mechanismu, jako je tomu při léčbě postnatální myokarditidy (21). AV blokádu imunoglobuliny ovlivnit nedokážou (23).

I když nedojde k úmrtí plodu, má novorozenec s kompletním AV blokem vysoké riziko implantace kardiostimulátoru (24) se všemi negativními důsledky (sternotomie s našitím epikardiálních elektrod, opakované výměny generátoru pacemakeru, riziko vývoje dilatační kardiomyopatie na podkladě proběhlé myokariditidy nebo indukované pacemakerem).

PREVENTIVNÍ LÉČBA

Úvahy o prevenci AV blokády se opírají o dokumentovanou konverzi neúplné formy blokády na sinusový rytmus (15). Aplikace kortikoidů matce může zvrátit progresi AV bloku 1. a 2. stupně ke kompletní formě, která je již ireverzibilní. Regrese kompletní AV blokády není spolehlivě prokázaná. Logicky správnou cestou by byla detekce plodů s AVB 1. stupně, kdy je prodloužený, ale stále zachovalý přenos vzruchu ze síní na komory. Vysoký výskyt (až 33 %) plodů s prodlouženým PQ intervalem séropozitivních matek byl dokumentován v jediném souboru (26), v dalších studiích nebyl potvrzen (27, 28). Z těchto studií navíc vyplývá, že fetální prodloužení PQ intervalu nepredikuje progresivní AV blokádu, a doklady o postupném rozvoji blokády jsou stále pouze předmětem ojedinělých kazuistik.

Na základě zkušeností a literárních údajů o zvýšeném riziku kompletní AV blokády u dalšího plodu (3, 6) jsme se rozhodli pro preventivní podávání transplacentárních glukokortikoidů u těhotných, které již v předchozí graviditě měly záchyt této arytmie. Postupovali jsme dle doporučení o léčebné dávce dexamethasonu (18). Tento postup jsme použili dosud celkem u 12 těhotných. Doufali jsme, že preventivní podání dexamethasonu jednoznačně zabrání vzniku AV blokády – již proto, že podobné léčebné schéma prokazatelně zastavilo rozvoj již probíhající nemoci (15, 26). Negativní zkušeností však bylo, že u 2/12 těhotných došlo k rychlé progresi AV bloku 3. stupně navzdory terapeutickým dávkám transplacentárně pronikajících gulokortikoidů. To poukazuje jednak na zjevně velikou agresivitu autoprotilátek, namířených proti AV uzlu, ale i na skutečnosti, že efektivita protizánětlivého účinku kortikoidů je značně omezená.

Nejlepší možnou prevencí kardiální postižení u lupus neonatorum plodu je zjevně efektivní léčba těhotné se systémovým onemocněním (29). Velmi slibným lékem v prevenci postižení plodu je hydroxychlorochin (Plaquenil), jak naznačily již pokusy na *in vitro* modelech. Limitované studie prokazují, že právě podávání léku používaného při léčbě malárie může snížit riziko vzniku AV blokády u plodu (30, 31).

DISPENZARIZACE TĚHOTNÉ

Bylo prokázáno, že hlavním rizikovým faktorem při vzniku AV blokády plodu je výše titru anti-Ro autoprotilátek, zejména anti-Ro 52 kDa. Jejich střední či významné zvýšení bylo signifikatně spojeno s vyšším rizikem AV blokády, nezávisle na titru anti-La autoprotilátek (8). Je tedy zřejmé, že právě tyto těhotné by měly být zvláště pečlivě sledovány.

Řada kazuistik a vlastní zkušenost ale jasně demonstrují, že k rozvoji kompletní AV blokády může dojít velmi rychle i za < 24 hodin (32). Z tohoto pohledu je frekvence sledování těhotných značně diskutabilní. Možným přístupem je domácí monitoring. Při něm si těhotná sama pomocí dopplerovského přístroje minimálně 2krát denně monitoruje srdeční frekvenci plodu. Při její nepravidelnosti či frekvenci mimo fyziologický limit je těhotná neprodleně vyšetřena a při průkazu AV blokády 1. nebo 2. stupně zahájena léčba kortikoidy a imunoglobuliny. Výsledky jsou velmi slibné, ale ani tak nedošlo k zábraně vzniku kompletní AV blokády u všech plodů (33).

VLASTNÍ ZKUŠENOSTI

V Dětském kardiocentru bylo v období 2001–2016 vyšetřeno a sledováno celkem 24 plodů s kompletní AV blokádou. Průměrná tepová frekvence v okamžiku diagnózy byla 58 ± 9,4 tepů/min. Diagnóza byla stanovena mezi 19. a 32. týdnem (medián 21 týdnů). Anti-Ro autoprotilátky byly přítomny u 18 z nich (75 %). Známky srdečního selhání byly přítomny u 15 z 24 plodů s AVB 3. stupně. Jedno těhotenství bylo ukončeno na základě přání rodičů a dva plody odumřely při rozsáhlém hydropsu. Dvacet jedna plodů bylo řádně porozeno v termínu, 15 vyžadovalo implantaci kardiostimulátoru v různém věku (1 den – 2 roky, medián 2 týdny).

V uvedeném období bylo vyšetřeno celkem 127 dalších těhotných, které byly poslány k vyšetření s pozitivními autoprotilátkami (dle posledního vyšetření). AV blokáda 1. stupně byla diagnostikována u deseti z nich, 6/10 bylo léčeno dexamethasonem, k dalšímu rozvoji AV blokády nedošlo. Kompletní AV blokáda se rozvinula u tří těhotných, pouze u jednoho plodu byl zjištěn při iniciálním vyšetření AV blok 1. stupně. Dva z nich byly vzhledem k AV blokádě u předchozího plodu preventivně neúspěšně léčeny dexamethasonem.

ZÁVĚR

Kardiální postižení u lupus neonatorum plodů je vzácné, ale může vést při kompletní AV blokádě

k intrauterinnímu srdečnímu selhání a úmrtí. Léčba kompletní AV blokády u plodu neexistuje. Při prevenci je důležitá stratifikace rizika těhotných, kde důležitou roli hraje výše titru anti-Ro52 autoprotilátek. Ani preventivní podání kortikoidů a/nebo imunoglobulinů nemusí zastavit rozvoj lupus neonatorum u plodu. Podávání hydroxychlorochinu v těhotenství může významně snížit riziko vzniku atrioventrikulárního bloku u plodu.

Konflikt zájmů: žádný.

Literatura

1. **Hubsher O, Batista N, Rivero S, et al.** Clinical and serological identification of 2 forms of complete heart block in children. J Rheumatol 1995; 22: 1352–1355.

2. **Ho YS, Esscher E, Anderson RH, et al.** Anatomy of congenital complete heart block and relation to maternal anti-Ro antibodies. Am J Cardiol 1986; 58: 291–294.

3. **Buyon JP, Hiebert R, Copel J, et al.** Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from the national lupus registry. J Am Coll Cardiol 1998; 31: 1658–1666.

4. **Nield LE, Silverman ED, Smallhorn JF, et al.** Endocardial fibroelastosis associated with maternal anti-Ro and anti-La antibodies in the absence of atrioventricular block. J Am Coll Cardiol 2002; 40(4): 796–802.

5. **Lynne EN, Silverman ED, Taylor GP, et al.** Maternal anti--Ro and anti-La antibody-associated endocardial fibroeastosis. Circulation 2002; 105: 843–848.

6. **Mofors J, Eliasson H, Ambrosi A, et al.** Comorbidity and long-term outcome in patients with congenital heart block and their siblings exposed to Roo/SSA autoantibodies in utero. Ann Rheum Dis 2019; 75: 595–703.

7. **van Bergen AH, Cuneo BF, Davis N.** Prospective echocardiographic evaluation of atrioventricular conduction in fetuses with maternal Sjogren´s antibodies. Am J Obstet Gynecol 2004; 191: 1014–1018.

8. **Jaeggi E, Laskin C, Hamilton R, et al.** The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythmematosus. J Am Coll Cardiol 2010; 24: 2778–2784.

9. **Salomonsson S, Dzikaite V, Zeffer E, et al.** A population-based investigation of the autoantibody profile in mothers of children with atrioventricular block. Scand J Immunol 2011; 74: 511–517.

10. **Anami A, Fukushima K, Takasaki Y, et al.** The predictive value of anti-SS-A antibodies titration in pregnant women with fetal congenital heart block. Mod Rheumatol 2013; 23: 653–658.

11. **Berg C, Geipel A, Kohl T, et al.** Atrioventricular block detected in fetal life: associated anomalies and potential prognostic markers. Ultrasound Obstet Gynecol 2005; 26: 4 –15.

12. **Eliasson H, Sonesson SE, Sharland G, et al.** Isolated atrioventricular block in the fetus: A retrospective, multinational, multicenter study of 175 patients. Circulation 2011; 124 (18): 1919–1926.

13. **Custodeat-Chalumeau N, Amoura Z, Le Thi Hong D, Piette JC.** Questions about dexamethason use for the prevention of anti-SSA related congenital heart block. Ann Rheum Dis 2003; 62: 1010–1012.

14. **Schmidt KG, Ulmer HE, Silverman NH, et al.** Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. J Am Coll Cardiol 1991; 17: 1360–1366.

15. **Mevorach D, Elchalal U, Rein AJ.** Prevention of complete heart block in children of mothers with anti-SSA/Ro and anit-SSB/La autoantibodies: detection and treatment of first degree atrioventricular block. Curr Opin Rheumatol 2009; 21(5): 478–482.

16. **Lee BH, Stoll BJ, McDonald SA, Higgins RD.** National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental outcomes of extremely low birth weight infants exposed prenatally to dexamethasone versus betamethasone. Pediatrics 2008; 121(2): 289–296.

17. **Rademaker KJ, de Vries WB.** Long-term effects of neonatal hydrocortisone treatment for chronic lung disease on the developing brain and heart. Semin Fetal Neonatal Med 2009; 14(3): 171–177.

18. **Jaeggi ET, Fouron JC, Silverman ED, et al.** Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 2004; 110: 1542–1548.

19. **Hickstein H, Kulz T, Claus R, et al.** Autoimunne-associated congenital heart block: treatment of the mother with immunoadsorption. Ther Apher Dial 2005; 9: 148–153.

20. **Makino S, Yonemoto H, Itoh S, Takeda S.** Effect of steroid administration and plasmapheresis to prevent fetal congenital heart block in patients with systemic lupus erythematosus and/or Sjogren's syndrome. Acta Obstetricia et Gynecologica 2007; 86: 1145–1146.

21. **Samuelsson A, Towers TL, Ravetch JV.** Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 2001; 291: 484–486.

22. **Friedman DM, Llanos C, Izmirly PM, et al.** Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Arthritis Rheum 2010; 62: 1138–1146.

23. **Pisoni CN, Brucato A, Ruffatti A, et al.** Failure of intravenous immunoglobulin to prevent congenital heart block: Findings of a multicenter, prospective, observational study. Arthritis Rheum 2010; 62: 1147–1152.

24. **Lopes LM, Tavares GM, Damiano AP, et al.** Perinatal outcome of fetal atrioventricular block: one-hundred-sixteen cases from a singleton institution. Circulation 2008; 118: 1268–1275.

25. **Jaeggi ET, Silverman ED, Yoo SJ, Kingdom J.** Is immune--mediated complete fetal atrioventricular block reversible by transplacental dexamethasone therapy? Ultrasound Obstet Gynecol 2004; 23(6): 602–605.

26. **Sonesson SE, Salomonsson S, Jacobsson LA, et al.** Signs of first-degree heart block occur in one-third of fetuse of pregnant women anti-SSA/Ro 52-kd antibodies. Arthirits Rheum 2004; 50: 1253–1261.

27. **Tomek V, Janoušek J, Reich O, et al.** Atrioventricular conduction time in foetuses assesed by Doppler echocardiography. Physiol Res 2011; 60: 611–616.

28. **Gardiner HM, Belmar C, Pasquini L, et al.** Fetal ECG: a novel predictor of atrioventricular block in anti-Ro positive pregnancies. Heart 2007; 93(11): 1454–1460.

29. **Saxena A, Izmirly PM, Mendez B, et al.** Prevention and treatment in utero of autoimmune associated congenital heart block. Cardiol Rev 2014; 22(6): 263–267.

30. **Izmirly PM, Custodeat-Chalumeau N, Pisoni CN, et al.** Maternal use of of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestation of neonatal lupus. Circulation 2012; 125: 76–82.

31. **Levy RA, Vilela VS, Cataldo MJ, et al.** Hydroxychloroquine in lupus pregnancy: A double-blind placebo controlled study. Lupus 2001; 10: 401–404.

32. **Cuneo BF, Ambrose SE, Tworetsky WT.** Detection and successful treatment of emergent anti-SSA-mediated fetal atrioventricular block. Am J Obstet Gynecol 2016; 215: 527–528.

33. **Cuneo BF, Sonesson SE, Levasseur S, et al.** Home monitoring for fetal heart rhtyhm during anti-Ro pregnancies. J Am Coll Cardiol 2018; 72(16): 1940–1951.

adresa pro korespondenci:

MUDr. Viktor Tomek, Ph.D.
Dětské kardiocentrum 2. LF UK a FN Motol
V Úvalu 84, 150 08 Praha 5
e-mail: viktor.tomek@fnmotol.cz