

Left Atrial Inexcitability in Children With Congenital Lupus-Induced Complete Atrioventricular Block

Sylvia Abadir, MD; Anne Fournier, MD; Suzanne J. Vobecky, MD; Charles V. Rohlicek, MD; Philippe Romeo, MD; Paul Khairy, MD, PhD

Background—Congenital atrioventricular block is a well-established immunologic complication of maternal systemic lupus erythematosus. We sought to further characterize the electrophysiological manifestations of maternal systemic lupus erythematosus on neonatal atria.

Methods and Results—Cases of isolated congenital atrioventricular block treated at our center over the past 41 years were identified. Data were extracted from clinical charts, pacemaker interrogations, ECGs, echocardiograms, and histopathological reports, when available. Of 31 patients with isolated congenital atrioventricular block, 18 were negative for maternal antibodies and had normal epicardial atrial sensing and pacing thresholds. In contrast, 12 of 13 patients with positive maternal antibodies had epicardial pacemakers, 5 (42%) of whom had left atrial (LA) inexcitability and/or atrial conduction delay. In 3 patients, the LA could not be captured despite high-output pacing. The fourth patient had acutely successful LA appendage and left ventricular lead placement. At early follow-up, an increased delay between the surface P-wave and intracardiac atrial depolarization was observed, indicative of atrial conduction delay. The fifth patient exhibited LA lead dysfunction, with atrial under-sensing and an increased capture threshold, 2 weeks after implantation. Biopsies of LA appendages performed in 2 patients showed no evidence of atrial fibrosis or loss of atrial myocytes.

Conclusions—Herein, we report previously undescribed yet prevalent electrophysiological ramifications of maternal systemic lupus erythematosus, which extend beyond congenital atrioventricular block to encompass alterations in LA conduction, including LA inexcitability. These manifestations can complicate epicardial pacemaker implantation in newborns. In the absence of histological evidence of extensive atrial fibrosis, immune-mediated functional impairment of electrical activity is suspected. (*J Am Heart Assoc.* 2015;4:e002676 doi: 10.1161/JAHA.115.002676)

Key Words: atrial inexcitability • atrioventricular block • congenital • interatrial block • maternal lupus

Cardiac manifestations are highly prevalent in patients with systemic lupus erythematosus (SLE).^{1,2} While electrical abnormalities can occur, isolated atrioventricular (AV) conduction disease, ranging from first degree to complete AV block (AVB), is rarely seen in older children and adults with SLE such that pacemakers are infrequently required.^{3–8} A few reports have described abnormal atrial

electrical activity in the form of atrial standstill, which was speculated to be secondary to recurrent flares of SLE, pericarditis, myocarditis, and/or myocardial arteritis.⁹ In contrast, complete AVB and ventricular cardiomyopathy are well-established immunologic complications in neonates of mothers with anti-Ro/SSA antibodies, such that pacemakers are frequently indicated. However, atrial conduction disorders, including atrial inexcitability or standstill, have not been described in this setting. We, therefore, sought to further characterize the electrophysiological manifestations of maternal SLE on neonatal atria.

Methods

We identified all patients diagnosed with congenital complete AVB in the absence of structural heart disease between June 1971 and December 2012 at Sainte Justine Hospital, Montreal, Canada. Within this cohort of patients, we further identified those in whom AVB was associated with maternal anti-SSA and/or anti-SSB antibodies. Data abstracted from

From the Divisions of Cardiology and Cardiac Surgery, CHU mère-enfant Sainte-Justine (S.A., A.F., S.J.V., P.K.) and Department of Medicine and Pathology, Montreal Heart Institute (P.R., P.K.), Université de Montréal, Quebec, Canada; Department of Cardiology, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada (S.A., C.V.R.).

Correspondence to: Paul Khairy, MD, PhD, Adult Congenital Heart Center, Montreal Heart Institute, 5000 Belanger St E, Montreal, Québec, Canada H1T 1C8. E-mail: paul.khairy@umontreal.ca

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medical records included demographic information, presence or absence of maternal autoimmune antibodies, details regarding pacemaker implantation and all re-interventions, pacemaker interrogations, ECGs, echocardiograms, and histopathological reports when available.

Continuous variables are expressed as median and interquartile range (25th, 75th percentile). Categorical data are summarized by frequencies and percentages. Inferential statistics were not conducted given the small sample size. The protocol was approved by the local institutional review board. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 31 patients were diagnosed with isolated congenital complete AVB (Figure 1), 13 (42%) of whom had positive maternal antibodies. Of the 18 patients without maternal anti-SSA/SSB antibodies, all underwent uneventful epicardial pacemaker implantation, with no reported difficulties associated with atrial sensing or pacing. All maintained normal atrial pacing and sensing thresholds on follow-up and none developed cardiomyopathy. Among the 13 patients with maternal antibody-mediated congenital complete AVB, 12 (92%) underwent pacemaker implantation (Table 1). A 1.5-year-old asymptomatic patient with complete AVB and a junctional escape rate >50 bpm did not yet receive a pacemaker. Five (42%) of the 12 patients with pacemakers were found to have notable atrial electrical abnormalities in

the setting of normal serum electrolytes. Characteristics of these 5 patients are summarized in Table 2 and their case presentations are further described below. All 5 underwent epicardial pacemaker implantation under general anesthesia, with bipolar steroid-eluting leads.

Patient 1

A baby girl, born at 36^{5/7} weeks, had fetal evidence of bradycardia at 21 weeks associated with first-degree AVB. Cardiac anatomy and function were normal, with no evidence of hydrops. Her mother was positive for lupus autoantibodies. Despite maternal treatment with dexamethasone, AVB progressed to complete block within a month. A small pericardial effusion with moderate biventricular AV valve regurgitation prompted a premature C-section. At birth, she had a junctional escape rhythm at 75 bpm. Postnatal echocardiography revealed resolution of the pericardial effusion and AV valve regurgitation.

A dual-chamber epicardial pacemaker was implanted at 1 month of age in the context of recurrence of the pericardial effusion, a junctional escape rate in the 60s, persistent pulmonary hypertension (50% of systemic systolic pressure) despite phosphodiesterase inhibitors, and failure to thrive. Atrial standstill was readily observed. The left atrial appendage (LAA) and left atrium (LA) appeared abnormally white (Figure 2). Appropriate sensing was possible but no capture could be achieved at high outputs. Thus, the atrial lead was placed on the right atrium (RA), and the ventricular lead on the left ventricle with good sensing and capture thresholds.

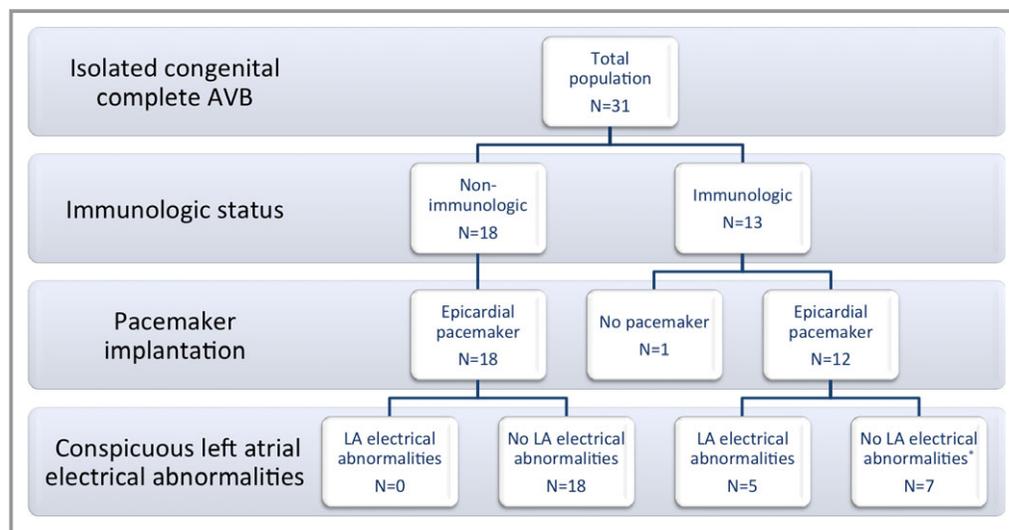


Figure 1. Distribution of cases of isolated congenital complete atrioventricular block. *Two patients with no known LA electrical abnormalities had a single-chamber ventricular pacemaker. Since LA pacing and sensing thresholds were not assessed, the prevalence of LA electrical abnormalities in patients with immunologic AVB may be underestimated. AVB indicates atrioventricular block; LA, left atrial.

Table 1. Characteristics of the 12 Patients With Isolated Immunologic Complete AVB and Pacemaker Implantation

	All Patients (N=12)	Atrial Electrical Abnormalities (N=5)	No Identified Atrial Electrical Abnormalities (N=7)
Female, N (%)	6 (50)	4 (80)	3 (43)
Maternal antibodies, N (%)			
Anti-SSA positive only	5 (42)	2 (40)	3 (43)
Anti-SSB positive only	1 (8)	1 (20)	0 (0)
Both positive	5 (42)	2 (40)	3 (43)
Diagnosis of AVB, N (%)			
Prenatal	6 (50)	4 (80)	3 (43)
Postnatal	6 (50)	1 (20)	4 (57)
Age at first pacemaker, mo*	12.2 (0–100.8)	15.4 (0.5–59.2)	6.1 (0–100.8)
Dual-chamber pacemaker, N (%)	10 (83)	5 (100)	5 (71)
Age at last follow-up, y*	9.1 (0–21.9)	1.7 (0–18.6)	10.5 (5.8–21.9)

AVB indicates atrioventricular block.

*Continuous variables are summarized by median and range values.

Although the immediate postoperative period was uneventful, the patient's condition suddenly deteriorated on the night of day 3. Following a feed, the patient became tachypneic and clamped, and died despite immediate and prolonged attempts at resuscitation. Pacemaker interrogation a few hours later showed no evidence of lead dysfunction. On cardiac autopsy, no macroscopic abnormalities were identified. Microscopic examination demonstrated the absence of a clear AV node, which was replaced by fibrous tissue. Nonspecific changes were noted of the LA and LAA consisting of a mild fibrous pericarditis associated with degenerative phenomena described as dark microdebris similar to calcic salts arranged in a fine layer close to the LA epicardium.

Patient 2

The second patient had bradycardia at 21 weeks of gestation. Fetal echocardiography showed no evidence of cardiac abnormalities or hydrops. The mother, who had a diagnosis of SLE with positive antibodies, was started on dexamethasone at 26 weeks. The patient was born at 37^{3/7} weeks by C-section in predominantly 2:1 AVB with a mean junctional escape rate of 65 bpm. The patient remained asymptomatic despite progression to complete AVB, with a gradually decreasing junctional escape rate to 44 bpm and progressive

left ventricular dilation (Z score of 4.9 for the left ventricular end-diastolic diameter), yet with a normal shortening fraction for age.

An epicardial dual-chamber pacemaker was implanted at 59 months of age through a left anterolateral thoracotomy. The LAA was found to be very pale and described as white. An epicardial bipolar lead was fixed on the LAA. Sensing was appropriate, but capture could not be achieved anywhere on the LAA or LA despite outputs up to 8 V at 0.52 ms. The atrial lead was, therefore, fixed to the right atrial appendage without difficulty. The ventricular lead was placed on the left ventricle with satisfactory testing values. Multiple biopsies of the LAA were performed, which showed no evidence of atrial fibrosis or loss of atrial myocytes. Left ventricular function remained normal on follow-up.

Patient 3

The third patient, a 3-year-old girl, was born to a woman with positive anti-SSA antibodies. She was diagnosed with first-degree AVB at 20 weeks of gestation, with no associated cardiac abnormalities or signs of hydrops. Although the mother was started on corticosteroids and treated until the 32nd week, AVB progressed to complete block. Labor was induced at 37^{6/7} weeks, with an uncomplicated vaginal delivery. At birth, she had a mean junctional escape rate of 70 bpm. Progressive signs of fatigue and decreased functional capacity prompted implantation of a dual-chamber epicardial pacemaker at 16 months of age via a left anterolateral thoracotomy. Although sensing was adequate over the LA, no capture could be achieved despite high-output pacing. The atrial lead was fixed to the right atrial appendage, where sensing and pacing thresholds were normal, and the second lead was placed on the left ventricle. The immediate postoperative course was uneventful, although left ventricular dysfunction developed insidiously.

At the age of 2½ years, she was hospitalized with fever, vomiting, and signs of heart failure, with a left ventricular ejection fraction of 20% and interventricular dyssynchrony. Rapid deterioration led to intubation and inotropic support. Two weeks after admission, she underwent pacemaker upgrade to a biventricular epicardial system by adding a right ventricular lead. Findings on ventricular myocardial biopsy were uninformative. Despite biventricular pacing and maximal medical therapy, her condition remained precarious. She underwent implantation of a left ventricular assist device at 2 years and 9 months, followed by uneventful cardiac transplantation 7 months later. A biopsy prior to transplantation was compatible with dilated cardiomyopathy, with no evidence of SLE-related myocarditis and no perivascular antibodies by immunofluorescence. Atrial tissue was not available for microscopic analysis.

Table 2. Characteristics of the 5 Patients With Immunologic Complete AVB and Left Atrial Electrical Abnormalities

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis	Antenatal	Antenatal	Antenatal	2.5 years	Antenatal
Sex	Female	Female	Female	Female	Male
Antenatal maternal dexamethasone	+	+	+	—	—
Age at pacemaker implantation (mo)	1.4	59.2	16.4	38.2	0.5
Maternal antibodies	antiSSA+antiSSB+	antiSSA+antiSSB+	antiSSA+	antiSSA+	antiSSB+
Cardiac defect at birth	ASD	—	—	—	—
Later cardiac manifestations	Pericardial effusion, PHT, AVVR	LV dilation	LV systolic dysfunction	LV systolic dysfunction	LV dilation
Macroscopic LAA/LA appearance	White	White	Normal	Normal	Normal
Type of epicardial pacemaker system	Dual	Dual	Dual	Dual	Dual
Lack of LA/LAA capture	+	+	+	—	—*
Pacing site	RA, LV	RAA, LV	RAA, LV	LAA, LV	LA, LV
Initial pacemaker programming	DDD 60 to 100 bpm; gradual increase in upper tracking rate thereafter	DDD 60 to 90 bpm; gradual increase in upper tracking rate thereafter	DDD 60 to 180 bpm	DDD 60 to 180 bpm	DDD 60 to 180 bpm; VVIR 120 bpm shortly after (atrial lead dysfunction)
Last follow-up	Deceased	Alive, well	Alive, upgrade to CRT, heart transplant	Alive, upgrade to CRT, atrial lead transferred from LAA to RA	Alive, transvenous dual-chamber pacemaker at 5 y

ASD indicates atrial septal defect; AVB, atrioventricular block; AVVR, atrioventricular valve regurgitation; CRT, cardiac resynchronization therapy; LA, left atrium; LAA, left atrial appendage; LV, left ventricle/ventricular; minus sign denotes no; PHT, pulmonary hypertension; plus sign denotes yes; RA, right atrium; RAA, right atrial appendage.

*LA capture was possible but with high pacing threshold.

Patient 4

The fourth patient, who is now 6 years old, was incidentally found to be in complete AVB block at 2.8 years of age. Her mean junctional escape rate by Holter monitoring was 39 bpm, with a maximum pause of 3.4 s. She was asymptomatic and had biventricular dilation (Z score of 3.5) with normal biventricular systolic function. Work-up revealed anti-SSA antibodies in her mother. An epicardial pacemaker was implanted at 3 years of age, with leads positioned on the LAA and left ventricle without complication. Pacemaker interrogation revealed marked delay between the onset of the surface P wave and the local LAA signal, suggestive of atrial conduction delay. Left ventricular function progressively decreased on follow-up, with a shortening fraction of 12% and ejection fraction of 25% 6 months later. One year after pacemaker implantation, the system was upgraded to epicardial cardiac resynchronization therapy, and the LAA lead was replaced by a right atrial lead (Figure 3). At last follow-up, her left ventricular systolic function had improved, with an

ejection fraction of 45% and shortening fraction of 22%. As shown in Figure 3C, a narrow paced QRS-complex was obtained with a PR interval of 120 ms.

Patient 5

The fifth patient was diagnosed with complete AVB at 25 weeks of gestation with escape rates around 70 bpm and normal cardiac anatomy and function. The mother was diagnosed with SLE and tested positive for anti-SSB antibodies. Vaginal delivery at 38 weeks was uncomplicated. Given ventricular escape rates progressing down to the low 60s, an epicardial dual-chamber pacemaker was implanted at 2 weeks of age, with the atrial lead placed on the LA. Sensing was adequate and the pacing threshold was 2 V at 0.5 ms. The second lead was placed onto the left ventricle with adequate sensing and pacing thresholds. Two weeks later, dysfunction of the atrial lead was noted with undersensing and an increased pacing threshold. The pacemaker was reprogrammed to a VVIR mode at 120 bpm. Progressive

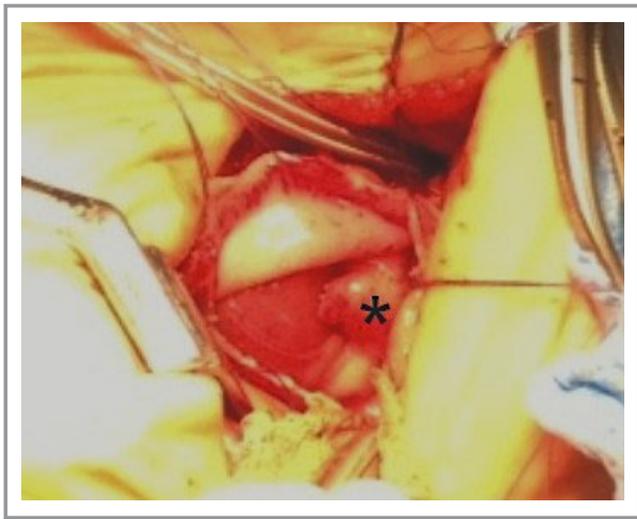


Figure 2. Surgical view for patient 1, through a left anterolateral thoracotomy and after reclining the pericardium (head of the patient to the right). The left atrium and left atrial appendage (*) appear white in color.

left ventricular dilation with mild systolic dysfunction was observed on follow-up, prompting initiation of an angiotensin-converting-enzyme inhibitor. When the generator required replacement at 5 years of age, a transvenous dual-chamber pacemaker system was implanted without complication.

Discussion

Herein, we report previously undescribed atrial electrical abnormalities in patients with isolated complete AVB in the setting of maternal SLE antibodies. Left atrial inexcitability and/or atrial conduction delay was highly prevalent (42%) in our series of patients with maternal anti-SSA and/or anti-SSB antibodies, in contrast to no patient with nonimmune-mediated AVB. Moreover, these atrial electrical anomalies were of clinical consequence and led to repositioning of the epicardial lead from the LAA/LA to the right atrial appendage/RA either at the initial intervention or during subsequent surgery.

Atrial Standstill and Intra-Atrial Conduction Delay

Persistent atrial standstill is characterized by a slow, often junctional, escape rhythm, with absent P waves by surface and endocavitary ECGs in combination with a lack of atrial excitability by direct electrical stimulation.¹⁰ The atrial inexcitability observed in our patients does not meet this definition since RA was not appreciably altered and normal surface P waves were observed. Rather, we report a limited form of atrial standstill confined to the LA. The concept of partial atrial standstill was previously reported in an adult

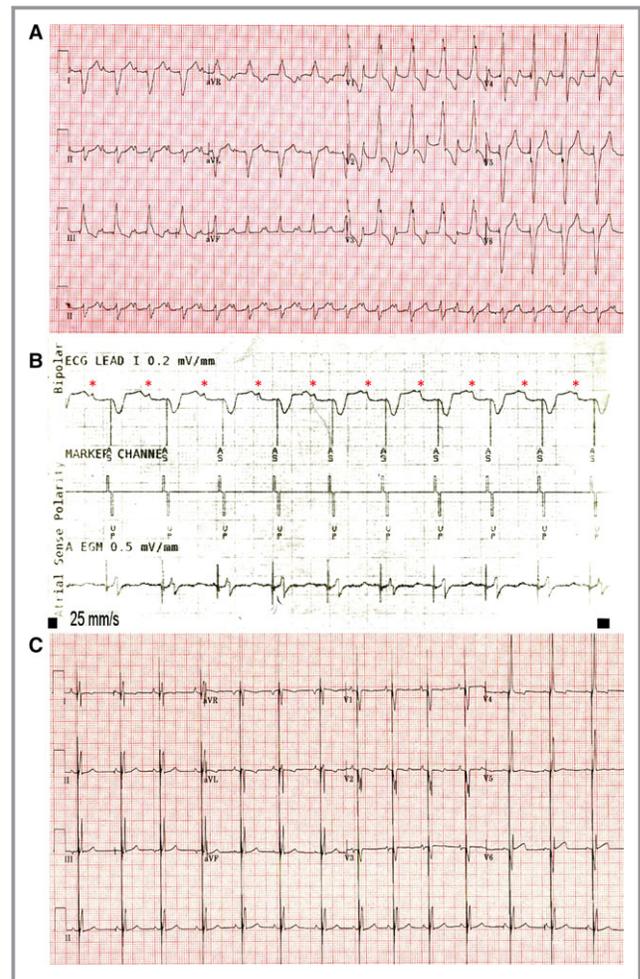


Figure 3. Patient 4. A, Standard 12-lead ECG after dual-chamber pacemaker implantation with the atrial lead implanted on the left atrial appendage. Sensed AV delay is programmed at 50 ms but the PR interval is 220 ms. B, Pacemaker interrogation with programmer strip showing bipolar signals (surface ECG lead I), marker channel, and A EGMs. Due to atrial conduction delay, a long interval (>200 ms) is noted between surface P waves (asterisks) and sensed atrial signals (AS on marker channel; local atrial signals on A EGM channel). C, Standard 12-lead ECG after upgrade to biventricular pacing system and transfer of the atrial lead to the high right atrium. The PR interval is 128 ms and the QRS complex is narrow (98 ms). A EGM indicates atrial electrogram; AV, atrioventricular.

without SLE who had absent P waves, with electrical and mechanical atrial activity confined to the LAA.¹¹

Atrial standstill in the fetus or infant is exceedingly rare.¹² To our knowledge, it has not previously been described in the context of immunologic or nonimmune-mediated AVB. Patients with chronic atrial stretch due to asynchronous pacing¹³ or atrial septal defects^{14,15} may demonstrate features of sinus node remodeling and atrial standstill. This raises the possibility that the atrial inexcitability observed in our patients was secondary to AVB and AV dyssynchrony as

opposed to a primary or immune-mediated pathophysiological mechanism. Nevertheless, the absence of atrial inexcitability observed in our series of patients without immune-mediated AVB argues against an atrial remodeling hypothesis.¹⁶

Inter-atrial conduction block occurs in $\approx 12\%$ of adults with AVB.¹⁷ It should be evaluated at the time of epicardial pacemaker implantation in order to optimize lead placement and AV delay programming.¹⁸

Electrical Abnormalities Without Major Histopathological Anomalies

The pale macroscopic appearance of the LA in 2 patients raised suspicion for endocardial fibroelastosis.¹⁹ However, histopathology was limited to non-specific changes. It remains possible that disease of a patchy nature might have been missed despite multiple biopsies directed at the grossly abnormal LA tissue. Alternatively, it may be hypothesized that functional abnormalities rather than anatomical defects underlie the observed electrical changes. In a recent series of 18 cardiac autopsies with neonatal lupus, no histological evidence of damage to the AV node or surrounding tissue was found in 2 cases with advanced AVB.²⁰ There is evidence to suggest that other electrical structures, such as the sinus node, can be affected in a functional way in patients with immunologic complete AVB.²⁰ For example, in a murine model of congenital AVB, maternal sera containing antibodies against SSA/Ro-SSB/La ribonucleoproteins inhibit L-type calcium channel currents in isolated cardiac myocytes and induce sinus bradycardia, without anatomical changes.²¹ Although the pathophysiology remains to be elucidated, a similar mechanism may potentially be implicated in our patients.

Mutations in the gene encoding the cardiac sodium channel alpha subunit, SCN5A, have been described in cases of familial atrial standstill²² and in a case with atrial standstill associated with progressive sinus node dysfunction and His-Purkinje system disease.²³ Genetic testing targeting sodium channel genes was not performed in our patients such that a genetic polymorphism leading to ion channel malfunctioning and atrial inexcitability cannot be excluded.

Electrical Abnormalities in the Offspring of Mothers With SLE

Conduction defects and cardiomyopathy are well-characterized immunologic complications of transplacental passage of maternal autoantibodies directed against fetal SSA/Ro or SSB/La ribonucleoproteins. These autoantibodies initiate a complex cascade of maternal antibody-triggered inflammation, ultimately leading to fibrosis and scarring.^{24–26} The incidence of AVB is estimated to be 2% for firstborns, with a recurrence risk of 16% to 18%.^{27–29} At least 50% to 66% of

afflicted children will require permanent pacing, often during the first year of life.^{27,30,31} The lack of previously reported LA inexcitability may reflect, in part, the fact that single-chamber ventricular pacemakers are often implanted. In our own series, 2 of 7 patients with immunologic AV block but considered not to have atrial electrical abnormalities underwent ventricular pacing only, such that the true incidence of LA inexcitability may be underestimated.

Prenatal diagnosis of maternal lupus-induced AVB was made in 4 of 5 of our patients with LA electrical abnormalities. In 2 such cases, corticosteroids were initiated once first-degree AVB was diagnosed but were ineffective. Despite some supportive evidence,³⁰ there is a lack of clear efficacy of steroids on arresting progression toward complete AVB. Moreover, the impact of steroids on atrial electrical disease remains unknown. Although several studies have reported that anti-SSA/Ro levels in maternal sera are associated with a high risk of cardiac complications,^{28,32} exact values were unavailable in our study, precluding correlations with atrial electrical disease. In fetal survivors with antibody-mediated AVB and normal cardiac function at birth, reported rates of later-onset dilated cardiomyopathy range from 5% to 10%.^{29,33} In our series, 5 of 12 patients (42%) with immunologic AVB and pacemaker implantation developed dilated cardiomyopathy. Larger studies are required to confirm the higher incidence of heart failure in the presence of atrial electrical disease.

Our institutional pacemaker programming strategy changed over the course of the study to reflect the literature, albeit limited, suggesting a link between faster ventricular pacing rates and cardiomyopathy in the setting of congenital AVB.³⁴ Two of 3 patients with DDD pacemakers initially programmed to track up to 180 bpm later received cardiac resynchronization therapy systems. In the 2 patients with the most recent device implantations, upper tracking rates were initially limited to 90 and 100 bpm, with subsequent 10-bpm increments on a monthly basis, if left ventricular function remained normal.

Preoperative Echocardiography

Preoperative echocardiograms performed in our patients did not systematically target LA or LAA mechanical contraction, such as with mitral Doppler inflow and mitral annulus tissue Doppler (A-wave and a'-wave, respectively). A previous report has described persistent LA mechanical standstill assessed by Doppler and tissue Doppler imaging in a 64-year-old patient with normal P-waves by ECG after a biatrial maze procedure for atrial fibrillation.³⁵ This case underscores our observation that LA inexcitability is not necessarily associated with the absence of P waves by ECG. It remains to be determined whether echocardiographic evaluation of LA and LAA function

in patients with immunologic AVB could guide the surgeon in selecting a different approach to the classic left anterolateral thoracotomy, in order to place the atrial lead on the RA rather than LA.

Conclusions

Electrical abnormalities of the LA and LAA appear to be common in patients with congenital lupus-induced AVB and include LA inexcitability and atrial conduction delay. The RA is seemingly spared from clinically recognizable electrical abnormalities and the surface P wave is not conspicuously altered. These LA electrical abnormalities bear clinical relevance, particularly with regard to influencing the selection of an epicardial atrial pacing site. To date, there is no histological evidence of extensive atrial fibrosis such that immune-mediated functional impairment of electrical activity is suspected. Further research is required to elucidate the underlying pathophysiological mechanism of this newly recognized entity, determine whether it may be diagnosed non-invasively such as by echocardiography, explore whether it is a marker of poorer outcome (eg, left ventricular systolic dysfunction), and assess whether directed therapies (eg, corticosteroids) may alter the disease course.

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Disclosures

None.

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