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

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**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). 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. 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. 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
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.
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 6/7 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 2 ½ 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         | 1.4       | 59.2      | 16.4      | 38.2      | 0.5       |
| implantation (mo)        |           |           |           |           |           |
| Maternal antibodies     | antiSSA+   | antiSSA+  | antiSSA+  | antiSSA+  | antiSSA+  |
|                         | antiSSB+   | antiSSA+  | antiSSB+  | antiSSB+  |
| Cardiac defect at birth  | ASD       | –         | –         | –         | –         |
|                         |           |           |           |           |           |
| Later cardiac           | Pericardial effusion, | LV dilation | LV systolic dysfunction | LV systolic dysfunction | LV dilation |
| manifestations          | PHT, AVIR |           |           |           |           |
| Macroscopic LAA/LA       | White     | White     | Normal    | Normal    | Normal    |
| appearance              |           |           |           |           |           |
| Type of epicardial       | Dual      | Dual      | Dual      | Dual      | Dual      |
| pacemaker system        |           |           |           |           |           |
| Lack of LA/LAA capture  | +         | +         | +         | –         | –         |
|                         |           |           |           |           |           |
| Pacing site              | RA, LV    | RAA, LV   | RAA, LV   | LAA, LV   | LA, LV    |
| Initial pacemaker        | DDD 60 to 100 bpm; | DDD 60 to 90 bpm; | DDD 60 to 180 bpm | DDD 60 to 180 bpm | DDD 60 to 180 bpm; |
| programming              | gradual increase in | gradual increase in | | | VVIR 120 bpm shortly |
|                         | upper tracking rate | upper tracking rate | | | after (atrial lead |
|                         | thereafter    | thereafter | | | dysfunction) |
| Last follow-up           | Deceased   | Alive, well | Alive, upgrade to CRT, | Alive, upgrade to CRT, | Alive, transvenous dual-chamber pacemaker at 5 y |
|                         |           |           | heart transplant | atrial lead transferred from LAA to RA | |

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

Atrial standstill in the fetus or infant is exceedingly rare. 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 pacing or atrial septal defects 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.\textsuperscript{16}

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

Electrical Abnormalities Without Major Histopathological Anomalies

The pale macroscopic appearance of the LA in 2 patients raised suspicion for endocardial fibroelastosis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{21} 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.\textsuperscript{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 standstill\textsuperscript{22} and in a case with atrial standstill associated with progressive sinus node dysfunction and His-Purkinje system disease.\textsuperscript{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.\textsuperscript{24–26} The incidence of AVB is estimated to be 2% for firstborns, with a recurrence risk of 16% to 18%.\textsuperscript{27–29} At least 50% to 66% of afflicted children will require permanent pacing, often during the first year of life.\textsuperscript{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,\textsuperscript{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,\textsuperscript{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%.\textsuperscript{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.\textsuperscript{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 bialarial maze procedure for atrial fibrillation.\textsuperscript{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 common in patients with congenital lupus-induced AVB and may alter the disease course.

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**Disclosures**

None.

**References**

1. Hejtmancik MR, Wright JC, Quint R, Jennings FL. The cardiovascular manifestations of systemic lupus erythematous. Am Heart J. 1964;68:119–130.

2. Tincani A, Rebaïoi CB, Taglietti M, Shoenfeld Y. Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. Rheumatology. 2006;45(suppl 4):iv8–iv13.

3. Bharati S, de la Fuente DJ, Kallen RJ, Freij Y, Lev M. Conduction system in lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. Arthritis Rheum. 1975;18:330–340.

4. Bilazarian SD, Taylor AJ, Brezinski D, Hochberg MC, Guarneri T, Provost TT. High-grade atrioventricular heart block in an adult with systemic lupus erythematosus: the association of nuclear RNP (U1 RNP) antibodies, a case report, and review of the literature. Arthritis Rheum. 1989;32:1170–1174.

5. Comin-Colet J, Sanchez-Corrall MA, Alegre-Sancho JJ, Valverde J, Lopez-Gomez D, Sabate X, Juan-Mas A, Esplugas E. Complete heart block in an adult with systemic lupus erythematosus and recent onset of hydroxychloroquine therapy. Lupus. 2001;10:59–62.

6. Godeau P, Guillevin L, Fechner J, Bloty O, Herrenman G. Disorders of conduction in lupus erythematous: frequency and incidence in a group of 112 patients. Ann Med Interne. 1981;132:234–240.

7. Liawatud S, Khan AJ, Nalamasu SR, Tan JI, Onwusanyi AE. Variable atrioventricular block in systemic lupus erythematosus. Clin Rheumatol. 2005;24:162–165.

8. Maier WP, Ramirez HE, Miller SB. Complete heart block as the initial manifestation of, systemic lupus erythematous. Arch Intern Med. 1987;147:170–171.

9. Hover AR, Koppes GM. Atrial standstill and complete heart block in systemic lupus erythematous. Chest. 1979;76:230–231.

10. Bloomfield DA, Sinclair-Smith BC. Persistent atrial standstill. Am J Med. 1965;39:335–340.

11. Demiralp E, Kirilmaz A, Cebeci BS, Ulusoy RE. Partial atrial standstill: a case report. J Electrocardiol. 2005;38:252–255.

12. Jaeggi ET, Chitayat D, Taylor G. Atrial standstill associated with loss of atrial myocytes: a rare cause of fetal bradyarrhythmia. Heart Rhythm. 2009;6:1370–1372.

13. Sparks PB, Mond HG, Vohra JK, Jayaprakash S, Kalman JM. Electrical remodeling of the atria following loss of atrioventricular synchrony: a long-term study in humans. Circulation. 1999;100:1894–1900.

14. Malav IC, Joneja R, Choudhary SK, Ramakrishnan S, Ray R, Jain A. Atrial standstill causing congestive heart failure in a child with ostium secundum atrial septal defect. Pediatr Cardiol. 2010;31:283–286.

15. Morton JB, Sanders P, Vohra JK, Sparks PB, Morgan JG, Spence SJ, Grigg LE, Kalman JM. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. Circulation. 2003;107:1775–1782.

16. Sanders P, Kalman JM. Progressive and persistent atrial inexcitability. Pacing Clin Electrophysiol. 2006;29:544–548.

17. Ausubel K, Klementowicz P, Furman S. Interatrial conduction during cardiac pacing. Pacing Clin Electrophysiol. 1996;9:1026–1031.

18. Parravicini U, Mezzani A, Bielli M, Di Camillo T, Pardo NF, Iraghi G, Zenone F, Zanetta M. DDD pacing and interatrial conduction block: importance of optimal AV interval setting. Pacing Clin Electrophysiol. 2000;23:1448–1450.

19. Nield LE, Silverman ED, Smallhorn JF, Taylor GP, Mullen JB, Benson LN, Hombrook LR. Endocardial fibroelastosis associated with maternal anti-Ro and anti-La antibodies in the absence of atrioventricular block. J Am Coll Cardiol. 2002;40:796–802.

20. Llanos C, Friedman DM, Saxena A, Izmiry PM, Tseng CE, Dische R, Abellar RG, Halushka M, Clancy RM, Buyon JP. Anatomical and pathological findings in hearts from fetuses and infants with cardiac manifestations of neonatal lupus. Rheumatology. 2012;51:1086–1092.

21. Qu Y, Baroudi G, Yue Y, Bourtidir M. Novel molecular mechanism involving alpha1D (Cav1.3) L-type calcium channel in autoimmune-associated sinus bradycardia. Circulation. 2005;111:3034–3041.

22. Makita N, Sasaki K, Groenewegen WA, Yokata T, Yokoshiki H, Murakami T, Tsutsui H. Congenital atrial standstill associated with coincheritance of a novel SCNA5A mutation and connexin 40 polymorphisms. Heart Rhythm. 2005;2:1128–1134.

23. Baskar S, Ackerman MJ, Clements D, Mayuga KA, Aziz PF. Compound heterozygous mutations in the SCN5A-encoded Nav1.5 cardiac sodium channel resulting in atrial standstill and His-Purkinje system disease. J Pediatr. 2014;165:1050–1052.

24. Briassouli P, Rifkin D, Clancy RM, Buyon JP. Binding of anti-SSA antibodies to apoptotic fetal cardiocytes stimulates urokinase plasminogen activator (uPA)/uPA receptor-dependent activation of TGF-beta and potentiates fibrosis. J Immunol. 2011;187:5392–5401.

25. Clancy RM, Kapur RP, Molad Y, Askanead AS, Buyon JP. Immunohistologic evidence supports apoptosis, IgG deposition, and novel macrophage/fibroblast crosstalk in the pathologic cascade leading to congenital heart block. Arthritis Rheum. 2004;50:173–182.

26. Taylor PV, Scott JS, Gerlis LM, Esscher E, Scott O. Maternal antibodies against fetal cardiac antigens in congenital complete heart block. N Engl J Med. 1986;315:672–676.

27. Buyon JP, Hiebert R, Copel J, Craft F, Friedman D, Katohi M, Lee LA, Provost TT, Reichlin M, Ruder L, Rupel A, Saleeb S, Weston WL, Skovron ML. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. J Am Coll Cardiol. 1998;31:1658–1666.

28. Ramsey-Goldman R, hom D, Deng JS, Ziegler GC, Kahle LE, Steen VD, LaPorte RE, Medsger TA Jr, Anti-SSA antibodies and fetal outcome in maternal systemic lupus erythematosus. Arthritis Rheum. 1986;29:1269–1273.

29. Wautlic J, Buyon JP. Autoantibody-associated congenital heart block: outcome in mothers and children. Ann Intern Med. 1994;120:544–551.

30. Saleeb S, Copel J, Friedman D, Buyon JP. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the research registry for neonatal lupus. Arthritis Rheum. 1999;42:2385–2345.
31. 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;39:130–137.

32. Jaeggi E, Laskin C, Hamilton R, Kingdom J, Silverman E. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus: a prospective study of 186 antibody-exposed fetuses and infants. J Am Coll Cardiol. 2010;55:2778–2784.

33. Moak JP, Barron KS, Hougen TJ, Wiles HB, Balaji S, Sreeram N, Cohen MH, Nordenberg A, Van Hare GF, Friedman RA, Perez M, Cecchin F, Schneider DS, Nehgme RA, Buyon JP. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol. 2001;37:238–242.

34. Chen CA, Chang CI, Wang JK, Lin MT, Chiu SN, Chiu HH, Wu MH. Restoration of cardiac function by setting the ventricular pacing at a lower range in an infant with congenital complete atrioventricular block and dilated cardiomyopathy. Int J Cardiol. 2008;131:e38–e40.

35. Kerut EK, McKinnie J, Reilly JP, Hanawalt C, Everson CT. Doppler evidence of persistent left atrial mechanical standstill with normal P-waves by electrocardiogram after biatrial CryoMaze procedure for atrial fibrillation. Echocardiography. 2011;28:809–811.