

Sinus Bradycardia, Wolff Parkinson White, and Left Ventricular Noncompaction

An Embryologic Connection?

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Abstract Left ventricular noncompaction (LVNC) is an uncommon disorder that has recently been recognized as a distinct cardiomyopathy. LVNC is thought to result from an arrest in the normal process of myocardial compaction. The association of Wolff-Parkinson-White with noncompaction of the left ventricle is well recognized. Sinus bradycardia has also been associated with LVNC, although less frequently than that of Wolff-Parkinson-White. We report an infant with LVNC, Wolff-Parkinson-White, and progressive sinus bradycardia who had a myocardial vascular abnormality in the region of the sinus node evident on autopsy. We propose that the progressive nature of the conduction system abnormality was as a result of abnormal angiogenesis.

Keywords Left ventricular noncompaction · Wolff-Parkinson-White · Bradycardia · Angiogenesis

Introduction

Left ventricular noncompaction (LVNC) is an uncommon disorder that has only recently been recognized as a distinct form of cardiomyopathy. LVNC is thought to result from an arrest in the normal process of myocardial compaction

resulting in abnormal left ventricular myocardial architecture. The clinical presentation is variable, but it is dominated by symptoms of congestive heart failure, arrhythmias, and systemic thromboemboli. The diagnosis of LVNC is based on the following echocardiographic criteria: (1) the presence of multiple echocardiographic trabeculations; (2) multiple intertrabecular recesses that communicate with the ventricular cavity as confirmed by color Doppler; (3) a noncompacted to compacted ratio of the endocardium of >1.4 [8]. The association of Wolff-Parkinson-White with noncompaction of the left ventricle is well recognized and has been described in up to 17% of pediatric patients with LVNC [4, 8]. Sinus bradycardia has also been associated with LVNC, although less frequently than that of Wolff-Parkinson-White [3, 4]. This report describes a 6-month-old infant with LVNC, Wolff-Parkinson-White, and progressive sinus bradycardia who had a myocardial vascular abnormality in the region of the sinus node evident on autopsy. The purpose of this article is to review LVNC and to propose that the progressive nature of the conduction system abnormality was as a result of abnormal angiogenesis.

Clinical History

Our patient is a 6-month-old, full-term male who presented shortly after birth with respiratory distress and cyanosis. The echocardiogram at birth was unremarkable; however, the electrocardiogram demonstrated Wolff-Parkinson-White. A 24-h ambulatory electrocardiogram showed normal heart rate variability, an average heart rate of 115 beats/min, and no arrhythmias. A transesophageal electrophysiology study performed at 6 weeks of age confirmed the diagnosis of Wolff-Parkinson-White. The antegrade

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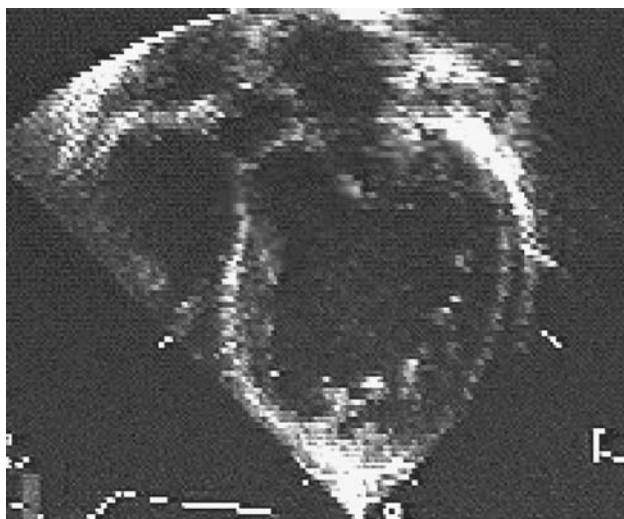


Fig. 1 Four-chambered echocardiographic view showing multiple trabeculations in the left ventricle

conduction characteristics of the accessory pathway were in the moderate-risk category. Following antegrade block in the accessory pathway, there was normal conduction through the atrioventricular node. There were no inducible arrhythmias during the electrophysiology study. An echocardiogram performed under sedation during the electrophysiology study revealed mild left ventricular hypertrophy with normal systolic function.

Over the next few months, serial echocardiograms demonstrated characteristic findings of LVNC (Figs. 1 and 2), as well as decreasing left ventricular systolic function. Additionally, serial ambulatory electrocardiograms showed progressive sinus bradycardia, with each one showing a lower average heart rate. The last ambulatory electrocardiogram performed at 5 months of age had an average heart rate of 75 beats/min with decreased heart rate variability.

Due to the association of cardiomyopathy with metabolic disorders, urine organic acids and serum amino acids were evaluated. There was a nonspecific elevation of urine 3 methyl glutaconic acid. The patient had no associated neutropenia. Unfortunately, at 6 months of age he developed abrupt respiratory distress and succumbed to his disease prior to confirmatory testing for Barth syndrome.

Autopsy examination included a detailed histologic evaluation of the conduction system, which showed no gross abnormalities. The cardiac muscle was over 1 cm thick, with prominent trabeculae in only the inner 20% of myocardium. However, there were focal channels that were compressed by myocardium that extended into 50% of the myocardium (Fig. 3), with microscopically persistent channels extending even deeper (Fig. 3 inset). There was also a thickened endocardium with an increase in fibrous tissue, indicating an element of fibroelastosis. Microscopic findings included ectatic vessels in the region of the sinus

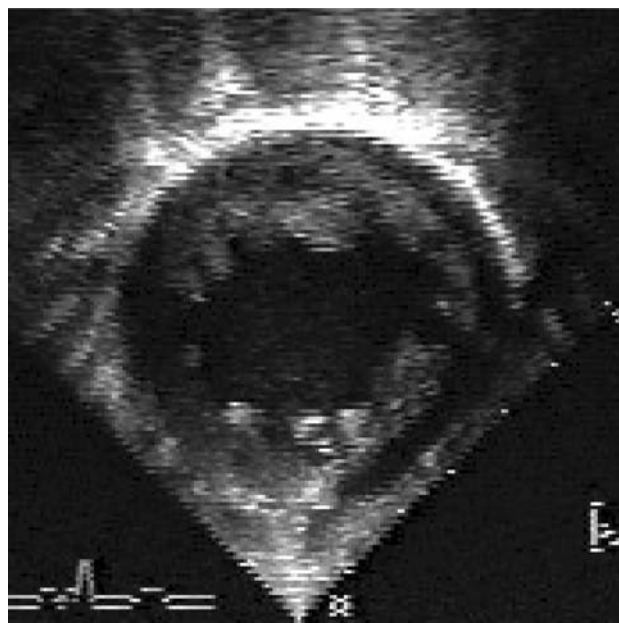


Fig. 2 Subcostal sagittal echocardiographic view of the left ventricle showing deep trabeculations

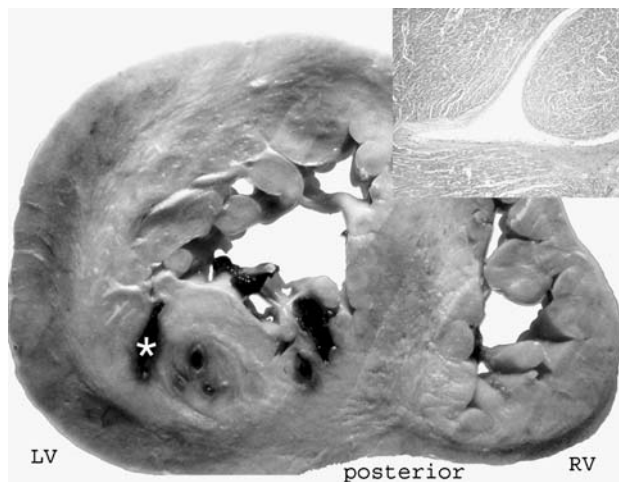


Fig. 3 Transverse section of heart demonstrating increased trabeculation in the left ventricle in superficial endocardium. There are dark, blood-filled sinuses, which indicate trabeculations reaching further into the myocardium, as shown in the histologic inset, where these sinuses are lined by fibroelastatic endocardium. LV: left ventricle; RV: right ventricle; * blood-filled sinus

node but not within the sinus node itself (Fig. 4). These vessels were significant in number but did not appear to be hemangiomatous. There was no evidence of fibrosis in the region of the sinus node, the atrioventricular node, or the bundle branches. Electron microscopy showed a markedly increased number of swollen mitochondria, which were noted to push aside myofibrils and raising suspicion for mitochondrial disease.

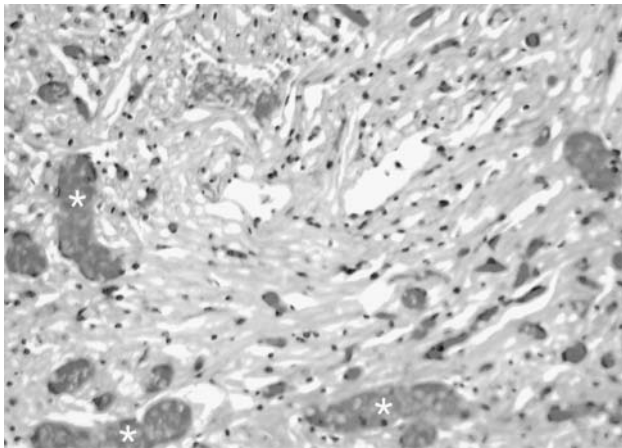


Fig. 4 High-power microscopic slide with hematoxylin and eosin stain of the atrial wall near the sinoatrial node with an excess number of small vessels, many of which are blood filled and dilated. * abnormal vessels

Discussion

Left ventricular noncompaction, as its name implies, typically affects the left ventricle, although right ventricular involvement has been described. During embryogenesis, the myocardium is an interwoven network of fibers that is in direct continuity with the left ventricular cavity. As the coronary artery circulation evolves between weeks 5 and 8 of embryonic life there is a simultaneous transformation of the spongy myocardium into compact musculature [2]. There are multiple neuroregulators and angiogenesis factors thought to be involved in the process of myocardial compaction; however, the details remain poorly characterized [11].

An undulating phenotype characterized by poor ventricular function with transient recovery of function followed by later deterioration has been described in patients with LVNC. Pignatelli et al. [8] proposed that specific gene mutations were responsible for individual variations in phenotype and that these fluctuations in systolic function might provide an explanation for those patients presenting as adults. Additionally, these authors found a high incidence of mitochondrial abnormalities in patients with LVNC [8]. Although our pathologic findings suggest a less severe form of LVNC by echocardiographic criteria, it does meet histologic criteria for LVNC based on a recent study that demonstrated that endocardial fibroelastosis is a characteristic histologic finding in noncompaction of the left ventricle [2]. The nonspecific mitochondrial abnormalities and the clotted blood within the left ventricular trabeculations also support the diagnosis of LVNC (Fig. 3).

The association of Wolff-Parkinson-White with noncompaction of the left ventricle is well recognized (Table 1). During embryogenesis there is direct continuity of the atrial and ventricular myocardium, which is ultimately disrupted

Table 1 Electrocardiographic abnormalities in LVNC

Study	No. of patients	Abnormal EKGs	WPW	Sinus bradycardia
Ichida et al. [4]	27	22 (88%)	4 (15%)	1 (4%)
Pignatelli et al. [8]	36	27 (75%)	6 (17%)	—
Wald et al. [10]	22	22 (100%)	1 (5%)	—
Celiker et al. [3]	11	10 (91%)	1 (9%)	6 (55%)

EKG = electrocardiogram

as the annulus fibrosus develops. Defects in the annulus fibrosus are thought to account for the formation of accessory pathways, particularly on the right side of the heart [7]. In ventricular noncompaction, the hypothesized arrest in development characterized by persistence of trabeculations might account for the persistence of myocardial channels between the atrium and ventricle, allowing the development of accessory pathways.

Sinus bradycardia has also been associated with LVNC (Table 1) and has been described in up to 55% of patients in one series [3]. There is evidence that coronary microcirculatory abnormalities might contribute to the development of ventricular dysfunction and susceptibility to arrhythmias, which are the major cause of morbidity and mortality in this population [5, 6]. However, the cause of conduction abnormalities, including sinus bradycardia, remains unclear.

It has been proposed that fibrosis might account for the progressive nature of atrioventricular (AV) block seen in patients with LVNC [6, 9]. Our patient did not have any fibrotic changes in the conduction system; however, there was evidence of an abnormal myocardial vascular supply in the region of the sinus node. We speculate that the underlying cause of the conduction defects in patients with LVNC might result from a primary defect in regional myocardial angiogenesis. Our patient had progressive sinus bradycardia and an abnormality of the vascular supply near the sinus node. In contrast, he had normal AV conduction, as confirmed by the electrophysiology study, with no microscopic abnormality of the vascular supply in the region of the AV node. This finding supports the idea that specific conduction defects might be at least in part related to abnormal angiogenesis. Perhaps abnormal angiogenesis prevents necessary signaling/transcription factors that are required to maintain the integrity of the conduction system. In a study by Aase et al. [1], mice were developed that carried a targeted deletion in vascular endothelial growth factor B gene, which is one of the angiogenic growth factors thought to be involved in the normal trabeculation process. Analysis of heart function by electrocardiogram showed that adult mice deficient in vascular endothelial growth factor B had an atrial conduction abnormality

characterized by a prolonged PR interval akin to first-degree AV block in humans. This research demonstrates the important physiologic interplay between angiogenesis and the conduction system. Although these mice had developmentally normal hearts, this study provides at least theoretical evidence supporting our speculation that the primary abnormality of the conduction in our patient was based on abnormal angiogenesis. This finding of abnormal myocardial vascular supply in the region of the sinus node in association with sinus bradycardia has not been previously documented.

Note added in proof. Following submission of the case report, a sibling was born with cardiomyopathy and sinus bradycardia. The echocardiogram at birth showed left ventricular hypertrophy with inconclusive evidence of left ventricular noncompaction. Skeletal muscle biopsy with electron microscopy showed abnormal mitochondria and further testing revealed a deficiency in cytochrome-*c* oxidase in the skeletal muscle fibers. Unfortunately, she succumbed to her disease awaiting cardiac transplantation and an autopsy was not performed.

References

1. Aase K, von Euler G, Li X, et al. (2001) Vascular endothelial growth factor-B-deficient mice display an atrial conduction defect. *Circulation* 104:358–364
2. Burke A, Mont E, Kutys R, Virmani R (2005) Left ventricular noncompaction: a pathological study of 14 cases. *Hum Pathol* 36:403–411
3. Celiker A, Ozkutlu S, Dilber E, Karagoz T (2005) Rhythm abnormalities in children with isolated ventricular noncompaction. *PACE* 28:1198–1202
4. Ichida F, Hamamichi Y, Miyawaki T, et al. (1999) Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. *J Am Coll Cardiol* 34:233–240
5. Jenni R, Wyss CA, Oeschelin EN, Kaufmann PA (2002) Isolated ventricular non compaction is associated with coronary micro-circulatory dysfunction. *J Am Coll Cardiol* 39:450–454
6. Junga G, Kneifel S, VonSmekal A, Steinert H, Bauersfeld U (1999) Myocardial ischemia in children with isolated non compaction. *Eur Heart J* 20:910–916
7. Lunel AAV (1972) Significance of the annulus fibrosis of heart in relation to AV conduction and ventricular activation in cases of Wolff Parkinson White. *Br Heart J* 34:1263–1271
8. Pignatelli RH, McMahon CJ, Dreyer WJ, et al. (2003) Clinical characterization of left ventricular noncompaction in children. A relatively common form of cardiomyopathy. *Circulation* 108:2672–2678
9. Robida A, Hajar HA (1996) Ventricular conduction defect in isolated non compaction of the ventricular myocardium. *Cardiology* 17:189–191
10. Wald R, Veldtman G, Golding F, Kirsh J (2004) Determinants of outcome in isolated ventricular noncompaction in childhood. *Am J Cardiol* 94:1581–1584
11. Zambrano E, Marshalko SJ, Jaffe CC, Hui P (2002) Isolated noncompaction of the ventricular myocardium: clinical and molecular aspects of a rare cardiomyopathy. *Lab Invest* 82:117–122