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【 CASE REPORT 】

Coexistence of Marfan-like Connective Tissue Disease with Morphologic Left Ventricular Non-compaction

Satomi Yashima[1], Hiroyuki Takaoka[1], Togo Iwahana[1], Manami Takahashi[1], Yusuke Kondo[1], Hideki Ueda[2], Aya Saito[3], Yuya Ito[3], Noboru Motomura[3], Nobuyuki Hiruta[4], Jun-ichiro Ikeda[5], Goro Matsumiya[2] and Yoshio Kobayashi[1]

Abstract:
We treated a man with co-incident Marfan-like connective tissue disease with morphologic left ventricular non-compaction (LVNC). He underwent valve-sparing aortic root replacement because of aortic root dilation at 43 years old. Pathological findings of the aorta revealed cystic medio-necrosis, consistent with Marfan syndrome. He developed congestive heart failure caused by LVNC at 47 years old. His daughter had scoliosis, and he had several physical characteristics suggestive of Marfan syndrome. We herein report a rare case of a patient who had Marfan-like connective disease with an LVNC appearance.

Key words: connective tissue disease, left ventricular non-compaction, Marfan syndrome

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Introduction

Left ventricular (LV) non-compaction (NC) is recognized as a myocardial disorder; however, the process of diagnosing and treating the disorder has not been well established, and almost 40% of affected patients have causative genetic mutations (1, 2). There is no specific therapy for patients with LVNC; however, anticoagulation or implantable cardioverter defibrillator or biventricular pacing therapy is sometimes performed in patients with LVNC (1).

Marfan syndrome is a genetic disorder that affects the connective tissues throughout the body and many parts of the body, including the aorta and heart. The prevalence of Marfan syndrome in the general population is 1 in 5,000 (2). Recently, a few case reports revealed the coexistence of LVNC and Marfan disease caused by fibrillin-1 gene mutations (2). Both LVNC and Marfan syndrome are rare diseases and have a risk of life-threatening adverse events, including heart failure or fatal arrhythmia. Their early detection and appropriate early intervention are necessary, and their coincidence should be more widely known.

We herein report a rare case of Marfan-like connective disease with an LVNC appearance.

Case Report

We treated a 47-year-old man with co-incident Marfan-like connective disease with an LVNC appearance. He had a history of left popliteal artery dissection at 36 years old. He had been diagnosed with moderate-severe aortic valve regurgitation with aortic root dilation on transthoracic echocardiography (TTE) because his electrocardiography revealed ST depression at a medical checkup and undergone valve-sparing aortic root replacement at 43 years old. Implantation of a permanent pacemaker was performed just after the procedure because of the incidence of complete atrioventricular block.

At this time, his LV function was already decreased, and his LV ejection fraction (LVEF) was almost 30%, but LVNC

[1]Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Japan, [2]Department of Cardiovascular Surgery, Chiba University Graduate School of Medicine, Japan, [3]Department of Cardiovascular Surgery, Toho University Sakura Medical Center, Japan, [4]Department of Surgical Pathology, Toho University Sakura Medical Center, Japan and [5]Department of Diagnostic Pathology, Chiba University Graduate School of Medicine, Japan
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Correspondence to Dr. Hiroyuki Takaoka, tapy21century@yahoo.co.jp

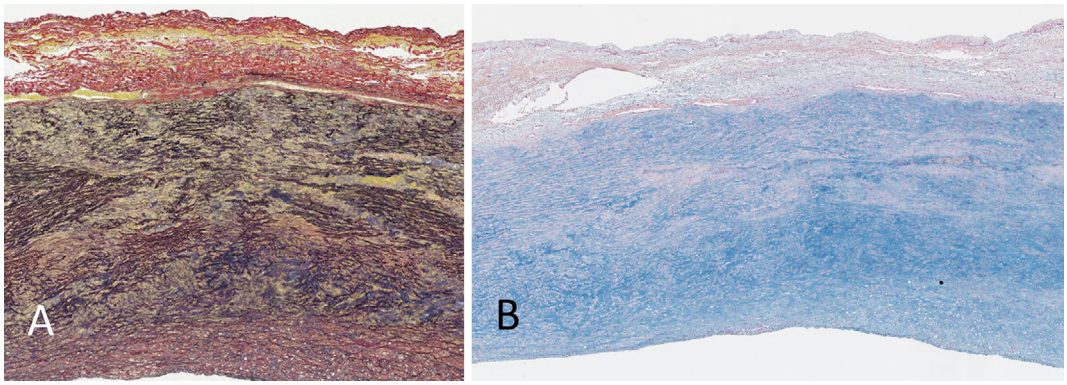

Figure 1. **Pathological findings of the ascending aorta. A: Pathological findings of the resected ascending aorta demonstrate elastic fibers of the middle membrane showing intermittent disturbance and a decrease followed by falling off as vesicles with myxoid degeneration following Elastica van Gieson staining. B: An increase in mucin is seen, but there is no inflammatory cell infiltration on Alcian blue staining. These pathological findings suggest cystic medionecrosis and are consistent with Marfan syndrome.**

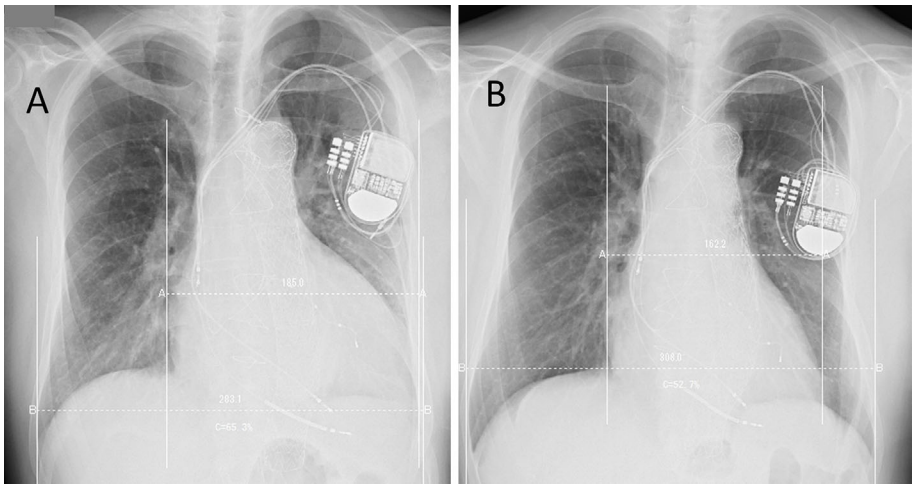

Figure 2. **Chest X-ray. A: Chest X-ray demonstrates cardiac enlargement with a cardiothoracic ratio of 65% at the beginning of biventricular pacing. B: Chest X-ray reveals an almost normalized cardiac size and cardiothoracic ratio of 52% almost 9 months after the start of biventricular pacing.**

was not detected on TTE. Pathological findings of the aorta during valve-sparing aortic root replacement revealed that the elastic fibers of the middle membrane showed intermittent disturbance and decreased and fell off as vesicles with myxoid degeneration following Elastica van Gieson staining (Fig. 1A). An increase in mucin was detected, but no inflammatory cell infiltration was noted following Alcian blue staining (Fig. 1B). These pathological findings suggested cystic medionecrosis and were consistent with Marfan syndrome. His TTE revealed that the LVEF, LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were 30%, 72 mm and 61 mm, respectively, just before the procedure and 30%, 65 mm and 56 mm almost 18 months after the procedure, respectively. Even after valve-sparing aortic root replacement and modification of aortic valve regurgitation, his LVEF did not improve, although the size of the LV slightly decreased.

He developed acute type B aortic dissection (DeBakey IIIB) at 45 years old, and stent graft implantation was performed because of the significant stenosis of the true lumen of the descending aorta and decrease in left ankle brachial index. After discharge, there was an increase in the serum brain natriuretic peptide (BNP) level to approximately 437 pg/mL, and LVNC was initially suspected on TTE. Cardiac enlargement on chest X-ray revealed progression of congestive heart failure (Fig. 2A), and TTE revealed LVNC. Administration of angiotensin-converting enzyme inhibitor and diuretic medicine was continued, and his dose of oral β-blocker was increased. Cardiac computed tomography (CT) was performed to screen for coronary artery stenosis just before admission because of the progression of heart failure, revealing marked endocardial trabeculations (Fig. 3A) with LV apical thrombus (Fig. 3B) and no significant coronary artery stenosis. Therefore, he was admitted to our hospital for the introduction of anticoagulant therapy and to upgrade from a dual chamber pacemaker to a biventricular-chamber

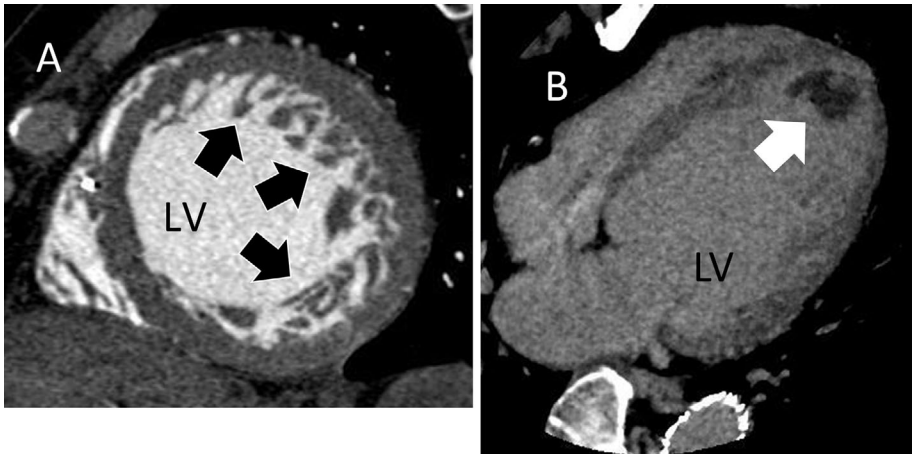

Figure 3. **Cardiac computed tomography performed just before admission. A: Marked endocardial trabeculations are clearly seen on the short-axial image (black arrows) in the early phase. B: Left ventricular apical thrombus is also seen on the long-axial image in the late phase (white arrow).**

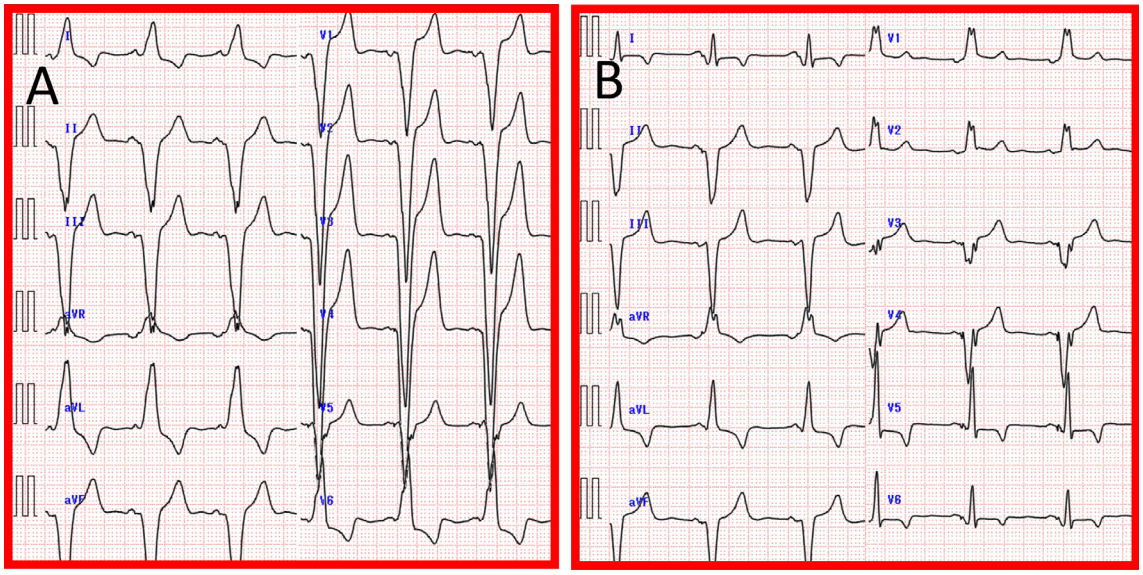

Figure 4. **Electrocardiography performed before and after the treatment in our institution. A: Electrocardiography just before treatment in our institution reveals left bundle branch block with P waves, which represents right ventricular pacing with atrial sensing. The QRS wave interval was 186 ms. B: Electrocardiography after upgrade to biventricular pacing reveals a decreased QRS wave interval of 140 ms.**

pacing with defibrillator system. His electrocardiogram (ECG) revealed a wide QRS because of the right ventricular pacing (Fig. 4A). His height and body weight were 181 cm and 73 kg, and his systolic/diastolic blood pressure, heart rate, body temperature and respiratory rate were 95/71 mmHg, 81 bpm, 36.1 °C and 16/minute at admission.

His daughter had scoliosis, and he had several physical characteristics (positive wrist and thumb sign, and reduced upper segment/lower segment ratio) suggestive of Marfan syndrome; however, the score for systemic features was only 4, and he did not want to undergo genetic testing; ultimately, he did not meet the latest criteria for Marfan syndrome (3). He did not have any other familial history of Marfan syndrome.

After the upgrade to cardiac resynchronization therapy (CRT), the QRS duration on his ECG decreased from 186 to 140 ms (Fig. 4B). TTE revealed an LVEF, LVEDD, LVESD, LV end-diastolic and end-systolic volume and ratio of the LV wall thickness of the noncompacted (NC) layer to the compacted (C) layer of 19% and 81 mm, 72 mm, 540 mL, 438 mL and 2.3 (13.5/5.5 mm), respectively, before the upgrade of CRT and 28%, 76 mm, 68 mm, 321 mL, 231 mL and 2.4 (14.2/5.8 mm), respectively, at almost 6 months after the upgrade of CRT (Fig. 5). His dyspnea on effort was alleviated after starting our treatment, his New York Heart Association grade changed from III to II, and his serum BNP level gradually decreased from approximately 250 to 70 pg/mL without any major adverse cardiac events, includ-

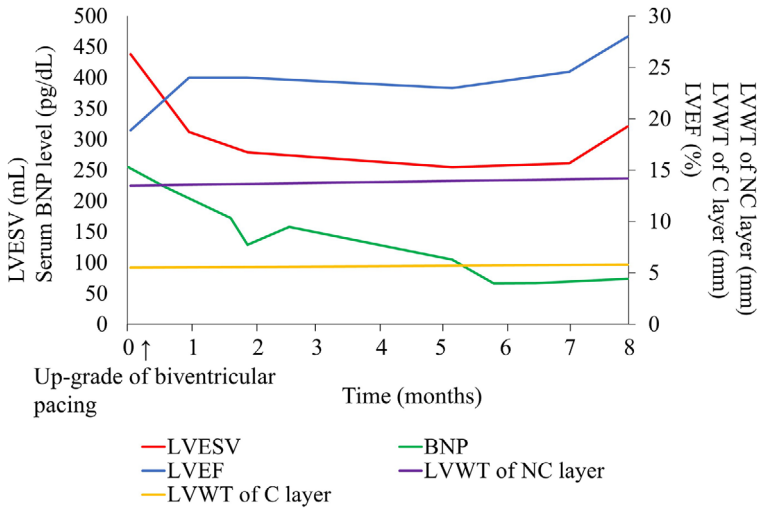

Figure 5. **Course of the serum brain natriuretic peptide levels, left ventricular (LV) end-systolic volume, LV ejection fraction and LV wall thickness of non-compacted and compacted layers on transthoracic echocardiography over almost 8 months after the upgrade to biventricular pacing. BNP: brain natriuretic peptide, LVESV: left ventricular (LV) end-systolic volume, LVEF: LV ejection fraction, LVWT of NC: LV wall thickness of the non-compacted layer, LVWT of C: LV wall thickness of the compacted layer**

ing ventricular tachy-arrhythmias (Fig. 5). Chest X-ray revealed a normalized cardiac size after the upgrade to dual-chamber pacing (Fig. 2B). Therefore, he was considered a responder of CRT based on the changes in the physical analysis and several examinations. He underwent endovascular aneurysm repair because of the abdominal aortic aneurysm and progression of dilatation of the descending aorta with type B chronic aortic dissection at 47 years old.

Discussion

LVNC is regarded as a rare genetic primary cardiomyopathy. It is a morphological disorder of excessive reticulated muscle formation and deep gaps in the ventricular myocardium with a prevalence of only 0.05-0.24% (4). There are several diagnostic criteria, but none are recognized as definitive. However, patients with a left ventricular myocardium (LVM), which is divided into two layers comprising the endocardial trabeculae-forming (NC) layer and epicardial dense (C) layer, with an NC/C ratio over 2 or 2.3 on TTE or magnetic resonance imaging (MRI) are usually diagnosed with LVNC (1).

Recently, the number of the patients with LVNC has increased because of the development of non-invasive diagnostic modalities. Some patients have no symptoms; however, the symptoms of NC can vary and include heart failure, arrhythmia and thrombosis, among others. Over 60% of patients have heart failure, and 20% have fatal arrhythmias. LVNC develops across a wide age range of patients, from newborns to the elderly. The process of myocardial compaction in the embryonic period is stopped and the sponge-like fetal myocardium is left behind. Finally, the myocardial dense layer is hypothesized not to be well established, but the exact mechanism remains unknown (1).

The involvement of genetic factors has been reported, and various causative genes have been identified. The involvement of sarcomere-related gene abnormalities is more common in adult cases than in pediatric cases, whereas an association with the causative gene of neuromuscular disease has also been reported (5). FBN1 is present in not only the myocardial extracellular matrix but also the valvular and vascular extracellular matrix (3, 6). Furthermore, abnormal FBN1 has been associated with LVNC in many reports showing such cardiac dysfunction in patients with Marfan syndrome (2). In a previous retrospective study of 51 patients with symptomatic LVNC, 10% (5 patients) had FBN1 genetic mutations, including 3 with symptoms that were clinically consistent with Marfan syndrome. These five patients did not have any other genetic abnormalities that could have caused LVNC. Based on this report, the specific genetic abnormality in Marfan syndrome (FBN1) was also considered to be a causative genetic abnormality in LVNC (5). Dilated cardiomyopathy is also recognized as a feature of Marfan syndrome, and fibrillin defect in the myocardium or increased aortic wall stiffness leading to increased LV afterload are considered causes of LV dilation (7).

LVNC is different from the other cardiomyopathies, and the risk of ventricular thrombi and adverse embolic events caused by these thrombi is relatively high; therefore, the early diagnosis and initiation of antithrombotic therapy is necessary in high-risk patients (1). The present patient had an LV apical thrombus on CT, but he did not develop any major adverse embolic events, including cerebral embolism. It is often difficult to detect LV thrombi, even using TTE, as in the present case; therefore, cardiac MRI should be per-

formed as soon as possible in cases with suspected LVNC (8). This is because the specificity of TTE for detecting LV thrombus is over 95%, but its sensitivity is only less than 40% (8). However, the specificity of MRI for detection of LV thrombus is almost 100%, and its sensitivity is also over 80% in MRI (8). Cardiac CT is also recommended for the evaluation of intra-cardiac masses if adequate images are not obtained by other noninvasive methods, based on the latest cardiac CT guideline (9). Therefore, CT is also useful especially in patients who are contraindicated for MRI because of cardiac devices or already scheduled to undergo CT for other reasons. The present case did not have renal dysfunction and had to undergo CT for the evaluation of aortic disease, so CT was a suitable alternative modality for the evaluation of LV apical thrombus. We retrospectively checked his findings of non-ECG-gated chest CT performed for the evaluation of his aorta almost one year before our detection of LV apical thrombus on cardiac CT. At that time, LV apical thrombus was already detectable, although it had not been detected on TTE.

A biventricular pacemaker was implanted in the present case because of the low LVEF on TTE and wide QRS waves on his ECG. In this case, the LVEF improved and left ventricular end-systolic volume (LVESV) decreased to almost 50% after dual-chamber pacing. The number of super-responders to dual-chamber pacing was previously reported to be higher in LVNC than in dilated cardiomyopathy (60% vs. 28%, respectively), the trend in LVNC was consistent with the outcome of this case (10). LVNC should be suspected in patients with both Marfan syndrome and a low LV function with wide QRS, and CRT may play a role in the treatment of heart failure in those patients. LVNC was not suspected during valve-sparing aortic root replacement, so AR might be one reason for the LV dysfunction in this case. However, the LVEF did not improve after the procedure, which was consistent with the fact that the low LV function in this patient was the initial change caused by LVNC. LVNC was detected after the worsening of LV dilatation following the procedure in this case, so the overdiagnosis of LVNC might be of some concern (11). However, even though LV dilatation improved after the initiation of CRT, LV hepertrabeculation did not regress, so we suspect that ought to have been diagnosed with LVNC.

Marfan syndrome affects the connective tissues of many parts of the body, and the cardiovascular problems it causes include aortic aneurysm or dissection and mitral valve regurgitation. The present case did not meet the criteria for Marfan syndrome; however, he did not undergo genetic testing. Despite the lack of genetic testing results, we should nevertheless follow up such patients carefully under a suspicion of Marfan syndrome. He required repetitive invasive treatments for aortic disease, and the aortic pathology seen during valve-sparing aortic root replacement was consistent with Marfan syndrome. Furthermore, his daughter had been diagnosed with scoliosis, and he had several systemic features suggestive of Marfan syndrome. Therefore, he should be treated similarly to a patient with Marfan syndrome. In patients with Marfan syndrome, early invasive treatment for aortic disease is sometimes necessary based on the guidelines (12); therefore, patients suspected of having Marfan syndrome based on several physical characteristics or the presence of LVNC but who do not wish to undergo genetic testing should be carefully treated in order to avoid missing the optimal timing for invasive treatment.

Conclusion

We treated a rare a case of a low LV function and intracardiac thrombus caused by LVNC during treatment of aortic disease caused by Marfan-like connective tissue disease. Both Marfan syndrome and LVNC are rare disorders, and their coincidence is even rarer; however, their potential co-occurrence should be known, and their early detection is important for preventing major adverse events caused by them.

The authors state that they have no Conflict of Interest (COI).

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References

1. Oechslin E, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? Eur Heart J **32**: 1446-1456, 2011.
2. Parent JJ, Towbin JA, Jefferies JL. Fibrillin-1 gene mutations in left ventricular non-compaction cardiomyopathy. Pediatr Cardiol **37**: 1123-1126, 2016.
3. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet **47**: 476-485, 2010.
4. Aryal MR, Badal M, Giri S, Pradhan R. Left ventricular noncompaction presenting with heart failure and intramural thrombus. BMJ Case Rep **2013**: 2013.
5. Ichida F. Left ventricular noncompaction. Circ J **73**: 19-26, 2009.
6. Bergman R, Nevet MJ, Gescheidt-Shoshany H, Pimienta AL, Reinstein E. Atrophic skin patches with abnormal elastic fibers as a presenting sign of the MASS phenotype associated with mutation in the fibrillin 1 gene. JAMA Dermatology **150**: 885-889, 2014.
7. Kahveci G, Erkol A, Yilmaz F. Dilated cardiomyopathy in a patient with Marfan syndrome accompanied by chronic type A aortic dissection and right atrial thrombus. Intern Med **49**: 2583-2586, 2010.
8. Weinsaft JW, Kim J, Medicherla CB, et al. Echocardiographic algorithm for post-myocardial infarction lv thrombus: a gatekeeper for thrombus evaluation by delayed enhancement CMR. JACC Cardiovasc Imaging **9**: 505-515, 2016.
9. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and In-

terventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol **56**: 1864-1894, 2010.

10. Bertini M, Ziacchi M, Biffi M, et al. Effects of cardiac resynchronization therapy on dilated cardiomyopathy with isolated ventricular non-compaction. Heart **97**: 295-300, 2011.

11. Gati S, Papadakis M, Papamichael ND, et al. Reversible *de novo* left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. Circulation **130**: 475-483, 2014.

12. Braverman AC, Harris KM, Kovacs RJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 7: aortic diseases, including Marfan syndrome: a scientific statement from the American Heart Association and American College of Cardiology. Circulation **132**: e303-e309, 2015.