

Hypertrophic Cardiomyopathy in a Monozygotic Twin Pair Similarly Different

Attila Kovács, MD, PhD*; Andrea Ágnes Molnár, MD, PhD*; Csilla Celeng, MD; Attila Tóth, MD; Hajnalka Vágó, MD, PhD; Astrid Apor, MD; Ádám Domonkos Tárnoki, MD, PhD; Dávid László Tárnoki, MD, PhD; János Kósa, PhD; Péter Lakatos, MD, PhD, DSc; Szilard Voros, MD; György Jermendy, MD, PhD, DSc; Béla Merkely, MD, PhD, DSc*; Pál Maurovich-Horvat, MD, PhD, MPH*

A 70-year-old female patient was admitted to our hospital because of atypical chest pain and fatigue. No relevant diseases were recorded in her previous medical history. During the physical examination, she presented with a mild systolic murmur. Her 12-lead ECG indicated right bundle branch block (Figure 1A), and blood pressure was normal. Initial blood test showed normal hs-Troponin T and D-dimer levels. Transthoracic echocardiography (TTE) revealed mild concentric left ventricular (LV) hypertrophy (end-diastolic interventricular septal thickness 14 mm; LV mass index, 96 g/m²) with septal bulging and mild aortic stenosis (transaortic mean gradient 18 mmHg, calculated aortic valve area 1.8 cm²) because of valve calcification (Figure 2A; Video I in the [Data Supplement](#)). In addition, TTE showed a good LV and right ventricular systolic function, impaired LV relaxation, and minimal mitral and tricuspidal regurgitation (Video II in the [Data Supplement](#)). To rule out obstructive coronary artery disease, we performed coronary artery calcium score scan and prospectively ECG-triggered coronary computed tomography angiography using a 256-slice multidetector-row computed tomography. The total coronary artery calcium score was 340; the calcium score of the aortic valve was 731 (Figure 3A). The coronary computed tomography angiography depicted a left dominant coronary system (Figure 4A) and several calcified and partially calcified atherosclerotic plaques along the left anterior descending coronary artery, causing moderate stenosis and partially calcified plaques in the left circumflex coronary artery, causing mild stenosis. The patient was discharged with optimized medications.

However, the patient had a monozygotic twin pair, who was diagnosed with aortic valve stenosis several years ago. Therefore, the sibling (second-born twin B) was asked to visit our hospital for further investigation. She was symptom-free, while presenting a moderate systolic murmur intensifying at the late systolic phase on auscultation. Her ECG showed

LV strain pattern (Figure 1B). The TTE examination of twin B revealed a typical pattern of hypertrophic obstructive cardiomyopathy: marked LV hypertrophy (end-diastolic interventricular septal thickness 18 mm; LV mass index, 123 g/m²) with systolic anterior motion of the mitral valve with subsequent significant dynamic LV outflow tract obstruction (peak gradient 91 mmHg) and mitral regurgitation (vena contracta width 7 mm; Figure 2B; Videos III and IV in the [Data Supplement](#)). Furthermore, the aortic valve was heavily calcified, suggesting a severe valvular stenosis (aortic valve area 0.6 cm² by planimetry). Mild aortic and tricuspid regurgitation was also present beside good LV and right ventricular systolic function and pseudonormal LV filling pattern.

The twin pair underwent cardiac magnetic resonance imaging to confirm the diagnosis of hypertrophic cardiomyopathy (HCM) in twin B and, possibly, in twin A (Figure 5). Cardiac magnetic resonance imaging examination of twin B showed LV hypertrophy with septal predominance (LV mass index 141 g/m², maximal end-diastolic wall thickness 27 mm; Figure 5F). Systolic magnetic resonance jet formation of the LV outflow tract was observed, and mitral regurgitation was detected in consequence of the systolic anterior motion phenomenon (Figure 5D and 5E). Aortic valve area was measured 0.7 cm². Interestingly, patchy midmyocardial late gadolinium enhancement was visible in the basal inferolateral segment. In twin A, cardiac magnetic resonance imaging confirmed a marked septal hypertrophy in the basal segments as well (LV mass index 134 g/m², maximal end-diastolic wall thickness 19 mm; Figure 5A). The midmyocardial contrast enhancement was also present in the basal inferolateral segment of the LV (Figure 5C). The presence of basal inferolateral late gadolinium enhancement is a rare coincidence with HCM; however, this late gadolinium enhancement pattern is often associated with rare diseases causing LV hypertrophy (ie, Anderson-Fabry, Danon disease).

Received March 3, 2016; accepted May 13, 2016.

From the MTA-SE Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest, Hungary (A.K., A.Á.M., C.C., A.T., H.V., A.A., B.M., P.M.-H.); Department of Radiology and Oncotherapy, Semmelweis University, Budapest, Hungary (Á.D.T., D.L.T.); PentaCore Laboratory, Budapest, Hungary (J.K.); First Department of Medicine, Semmelweis University, Budapest, Hungary (P.L.); Global Genomics Group (G3), Richmond, VA (S.V.); and III Department of Internal Medicine, Bajcsy-Zsilinszky Hospital, Budapest, Hungary (G.J.).

*Drs Kovács, Molnár, Merkely, and Maurovich-Horvat contributed equally to this work.

The [Data Supplement](#) is available at <http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.116.004794/-/DC1>.

Correspondence to Pál Maurovich-Horvat, MD, PhD, MPH, Városmajor St 68, H-1122, Budapest, Hungary. E-mail p.maurovich-horvat@cirg.hu (*Circ Cardiovasc Imaging*. 2016;9:e004794. DOI: 10.1161/CIRCIMAGING.116.004794.)

© 2016 American Heart Association, Inc.

Circ Cardiovasc Imaging is available at <http://circimaging.ahajournals.org>

DOI: 10.1161/CIRCIMAGING.116.004794

We performed coronary computed tomography angiography in twin B as well. Interestingly, twin B had a right dominant coronary system (Figure 4B). She had a higher plaque burden; calcified and partially calcified plaques were visible along the left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery, which caused moderate stenosis. Coronary artery calcium score and the calcium score of aortic valve were higher compared with twin A (665 and 1125, respectively; Figure 3B).

Genetic testing (TruSight One, Illumina, San Diego, CA) confirmed the monozygosity of the twins. A rare mutation in titin gene was revealed (TTN p. T8334M) in both siblings, which might be linked to the phenotype of HCM.¹ Interestingly, a mutation of desmoplakin gene was also found (DSP p. R908H), but none of the imaging modalities or medical history supported the presence of arrhythmogenic right ventricular cardiomyopathy. The presence of Anderson–Fabry or Danon diseases was excluded.

Holter monitoring revealed no arrhythmic events. Because of the lack of any complaints, no surgical procedure or ICD implantation (risk of sudden cardiac death: 3.93%) was indicated for twin B.² A second TTE was performed in twin A, which confirmed the lack of provokable outflow tract obstruction. The twin pair was discharged with optimal medication therapy, and yearly follow-up was advised. Echocardiographic screening of the family revealed no other affected relatives.

Discussion

We report a case of a monozygotic twin pair with different presentation of several cardiac phenotypes, including HCM, valvular calcification, and coronary dominance. Despite the existing genetic susceptibility of both siblings, only twin B presented the typical manifestation of HCM by TTE, which highlights the superior diagnostic utility of cardiac magnetic resonance imaging.³ The differing phenotype might be attributable to the severe aortic stenosis because the increasing afterload could lead to a greater extent of myocardial hypertrophy. The appearance of systolic anterior motion phenomenon also could worsen this process in twin B. Postnatal cardiovascular risk factors for the progression of valvular calcification are well-known; however, we could not reveal any major differences in medical history, lifestyle

habits, or environmental circumstances of the twin pair. The anthropometric parameters were similar (height, 164 versus 164 cm; weight, 77.3 versus 75.6 kg; BMI, 28.7 versus 28.1 kg/m²; twin A versus B, respectively). Occupation of both siblings involved light physical work until retirement, and both twins live in the countryside. Twin A gave birth to a boy and a girl, twin B to 2 girls per vias naturales. Both of them had menopause at the age of 56 years. They had no hypertension, hyperlipidemia, diabetes mellitus, and they were nonsmokers throughout their life. Twin B was on β -blocker, salicylate, and statin therapy since she was diagnosed with aortic valve stenosis. Notably, the dominance of the coronary tree was also dissimilar. Epigenetic (especially stochastic) effects and individual alterations of the intrauterine environment may affect the early development of the heart, providing a possible explanation for these differences.

In conclusion, our case report suggests a relevant epigenetic and environmental influence on different cardiovascular traits. Genetic determination to HCM alone may not lead to definite manifestation of the disease.

Disclosures

None.

References

1. Lopes LR, Zekavati A, Syrris P, Hubank M, Giambartolomei C, Dalageorgou C, Jenkins S, McKenna W, Plagnol V, Elliott PM; UK10K Consortium. Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing. *J Med Genet*. 2013;50:228–239. doi: 10.1136/jmedgenet-2012-101270.
2. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733–2779.
3. Maron BJ, Haas TS, Lesser JR. Images in cardiovascular medicine. Diagnostic utility of cardiac magnetic resonance imaging in monozygotic twins with hypertrophic cardiomyopathy and identical pattern of left ventricular hypertrophy. *Circulation*. 2007;115:e627–e628. doi: 10.1161/CIRCULATIONAHA.106.680512.

KEY WORDS: calcification ■ cardiovascular imaging ■ coronary computed tomography angiography ■ echocardiography ■ hypertrophic cardiomyopathy

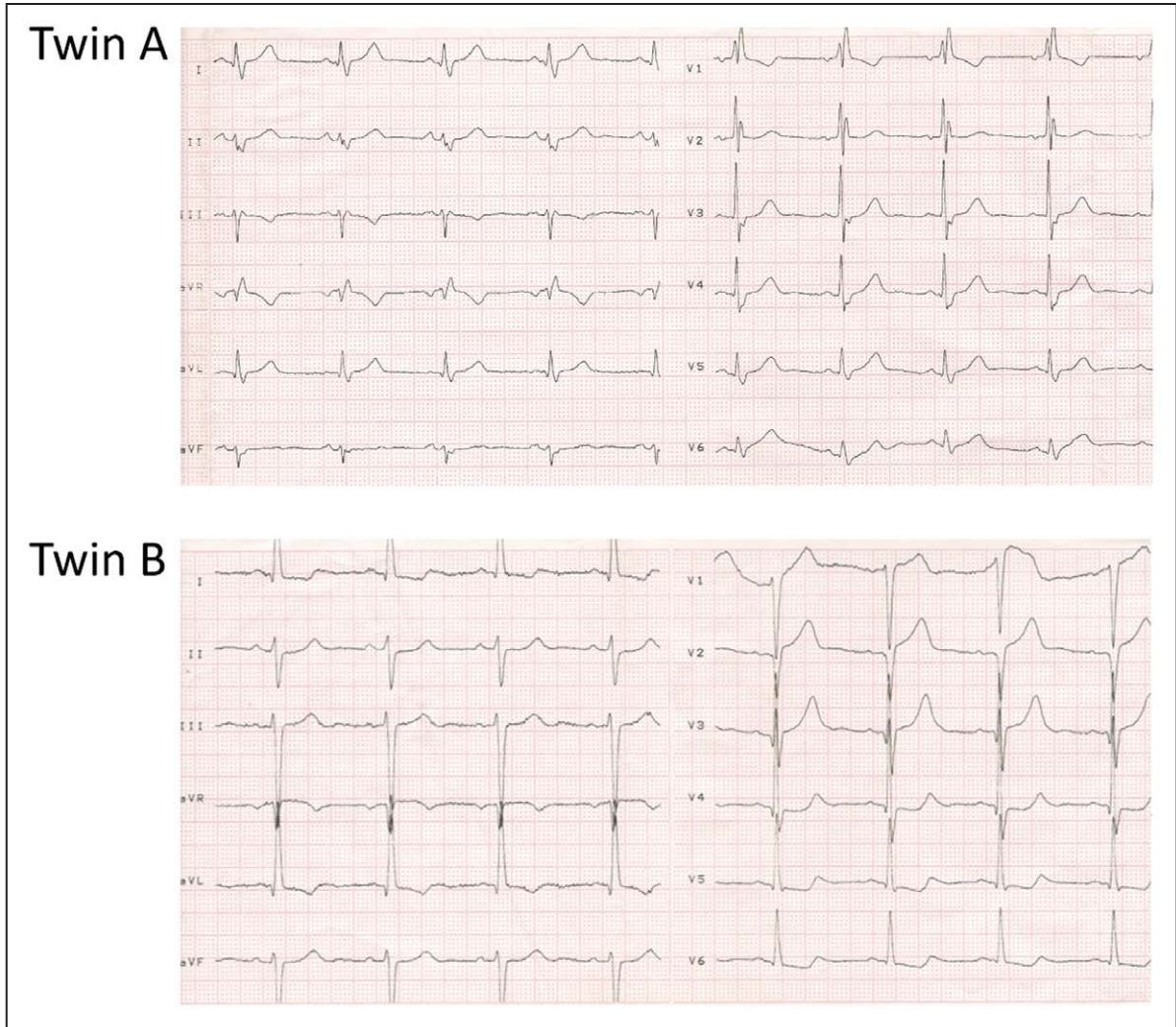


Figure 1. Twelve-lead ECG indicated right bundle branch block in twin A and left ventricular strain pattern in twin B.

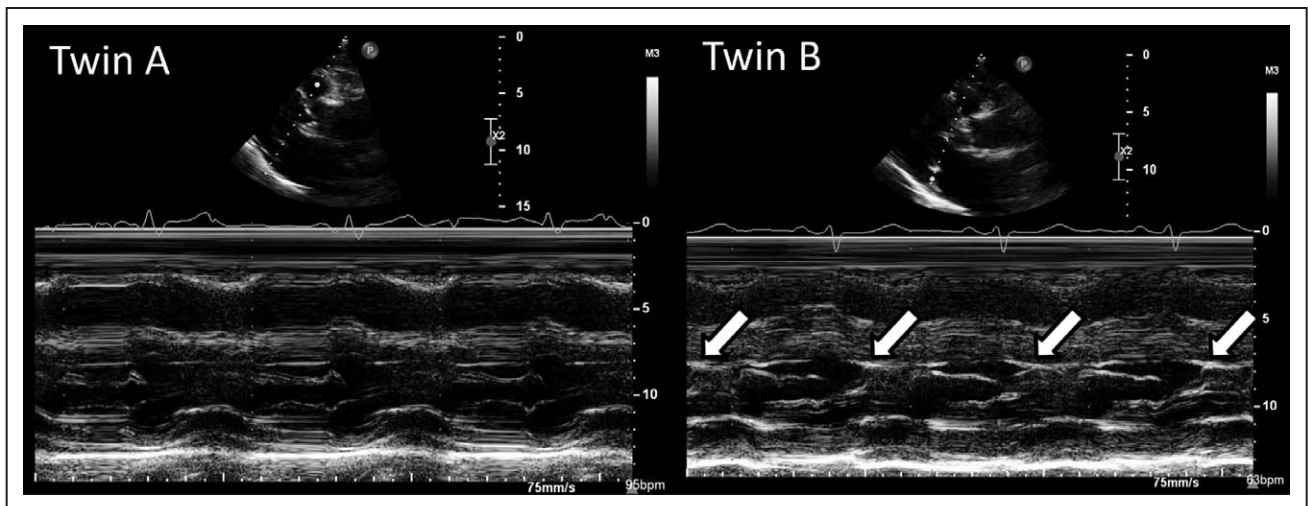


Figure 2. M-mode echocardiography shows systolic anterior motion of the mitral valve in twin B (arrows), which is absent in twin A.

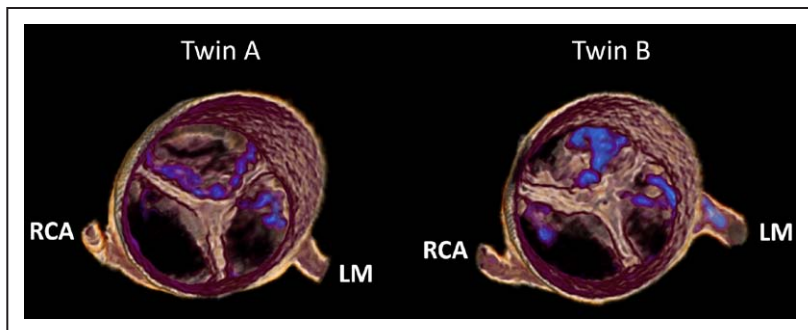


Figure 3. Volume-rendered images of the aortic root show aortic valve calcification (blue-violet color) with calcium score of 731 for twin **A** and calcium score of 1125 for twin **B**. LM indicates left main coronary artery; and RCA, right coronary artery.

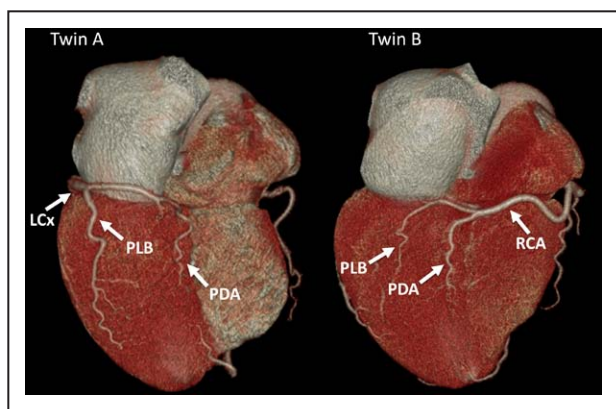


Figure 4. Volume-rendered image of twin **A** depicts a left dominant coronary system, whereas in twin **B**, a right dominant coronary system is visible. LCx indicates left circumflex artery; PDA, posterior descending artery; PLB, posterolateral branch; and RCA, right coronary artery.

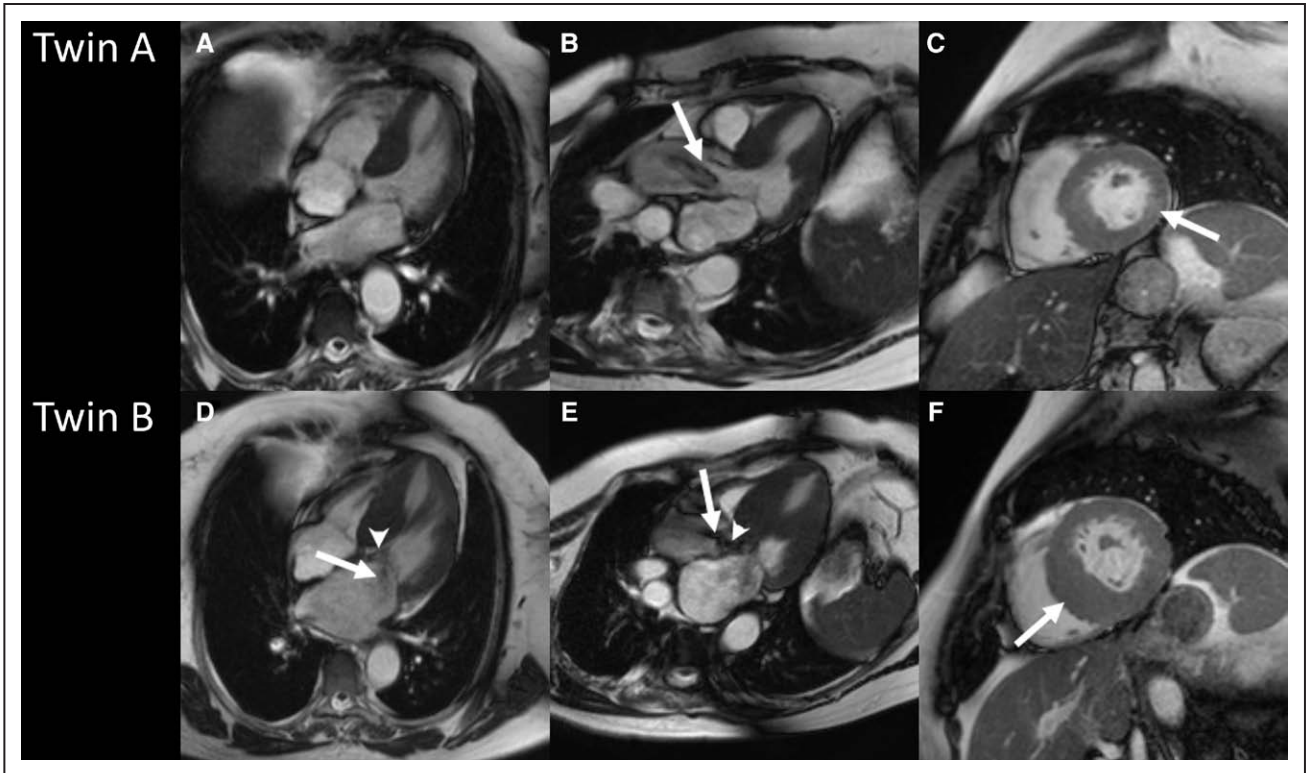


Figure 5. Cardiac magnetic resonance images of twin **A** (**A–C**) and twin **B** (**D–F**). Twin **B** shows more pronounced hypertrophy, more severe aortic valve stenosis, and systolic anterior motion (SAM) of the mitral valve. **A**, Four-chamber (4CH) balanced fast field echo (FFE) image in systolic phase. No outflow tract obstruction could be visualized for this twin. **B**, Left ventricular outflow tract (LVOT) balanced FFE image in systolic phase. Lack of SAM, no mitral valve insufficiency. White arrow points at the jet caused by the aortic stenosis. **C**, Short-axis (SA) balanced FFE image in diastolic phase. White arrow points at the basal inferolateral contrast enhancement. **D**, 4CH balanced FFE image in systolic phase. White arrowhead points at the outflow tract obstruction jet, white arrow at the mitral valve regurgitation caused by SAM. **E**, LVOT balanced FFE image in systolic phase. White arrowhead points at the jet formation caused by the outflow tract obstruction, white arrow at the jet by the aortic stenosis. **F**, SA balanced FFE image in diastolic phase. White arrow points at the thickened septal myocardium.

Hypertrophic Cardiomyopathy in a Monozygotic Twin Pair: Similarly Different

Attila Kovács, Andrea Ágnes Molnár, Csilla Celeng, Attila Tóth, Hajnalka Vágó, Astrid Apor, Ádám Domonkos Tárnoki, Dávid László Tárnoki, János Kósa, Péter Lakatos, Szilard Voros, György Jermendy, Béla Merkely and Pál Maurovich-Horvat

Circ Cardiovasc Imaging. 2016;9:

doi: 10.1161/CIRCIMAGING.116.004794

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2016 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circimaging.ahajournals.org/content/9/6/e004794>

Data Supplement (unedited) at:

<http://circimaging.ahajournals.org/content/suppl/2016/06/03/CIRCIMAGING.116.004794.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Imaging* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Imaging* is online at:
<http://circimaging.ahajournals.org/subscriptions/>

Supplemental Material

Video Legends

Video 1. Parasternal long-axis view with color Doppler of twin A shows mild aortic valve calcification and no flow acceleration in the left ventricular outflow tract.

Video 2. Apical four-chamber view with color Doppler of twin A depicts mild left ventricular hypertrophy, mild mitral regurgitation, no intracavitary flow acceleration.

Video 3. Parasternal long-axis view with color Doppler of twin B shows severe aortic valve calcification and systolic anterior motion of the mitral valve with subsequent flow acceleration in the left ventricular outflow tract and mitral regurgitation.

Video 4. Apical four-chamber view with color Doppler of twin B depicts marked left ventricular hypertrophy, mitral regurgitation and intracavitary flow acceleration due to the systolic anterior motion of the mitral valve.