45-year-old man with hypertrophic cardiomyopathy after alcohol ablation, progression to dilated cardiomyopathy (RCD code: III-1B.8a)

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common inheritable cardiac disorder with an estimated prevalence of 1:500 in the general population. In minority of patients, with the prevalence approximately of 3–5%, HCM progresses into dilated, end-stage or burn-out phase, characterized by LV wall thinning, systolic dysfunction and LV cavity dilatation. We present a case of a 45 year-old man with end-stage HCM with postcapillary pulmonary hypertension, who was experimentally treated with sildenafil. It resulted in noticeable clinical and haemodynamical improvement. JRCD 2014; 2 (1): 23–26

Key words: cardiomyopathy, sildenafil, end-stage

Background

Hypertrophic cardiomyopathy (HCM) is the most common inheritable cardiac disorder with an estimated prevalence of 1:500 in the general population [1,2]. Over 600 mutations were identified mostly in sarcomeric genes [2], which are usually passed on in an autosomal dominant mode of inheritance. These mutations disturb the genes encoding proteins of the cardiac sarcomere which leads to impaired function of the cardiomyocytes. The hallmark of HCM is left ventricular hypertrophy (LVH). There is a wide range of phenotypic expression of LVH, the most common pattern is asymmetric involvement of the inter-ventricular septum. Most cases of HCM begins to manifest in adolescence or early adulthood [3]. HCM may be a clinically silent disease but more often it reveals itself as a diastolic dysfunction, left ventricular outflow tract (LVOT) obstruction, supra-ventricular/ventricular arrhythmias or sudden cardiac death (SCD) [1]. In great majority of patients systolic function is either supra-normal or only mildly depressed. However, in minority of patients, with the prevalence approximately of 3–5%, HCM progresses into dilated, end-stage or burn-out phase, characterized by left ventricular (LV) wall thinning, systolic dysfunction and LV cavity dilatation [4,8]. Such a phenomenon resembles morphologic features of dilated cardiomyopathy and is called the dilated phase of HCM [5]. Clinically, dilated and hypokinetic LV leads to the development of progressive, systolic heart failure (SHF) that in most cases is indistinguishable from other forms of SHF.
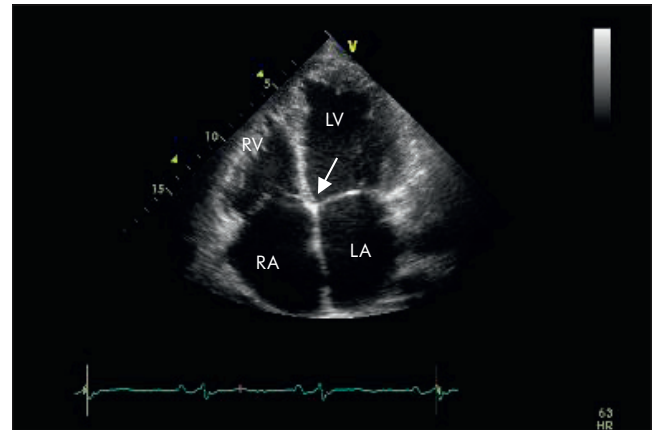
Case report

We report the case of 45-year-old male with HCM in the stadium of LV dilatation and systolic dysfunction who was admitted to our Centre due to acute decompensation of HF. He was diagnosed with HCM when he was 32 years old. He had abnormalities in 12-lead ECG during the routine examination in his work, therefore he was sent to the cardiologist. Earlier, he had been practising combat sports and body building exercises but denies usage of anabolics or other illegal substances. His family history was unremarkable. Initially, he had significant LVOT obstruction with a resting gradient exceeding 70 mm Hg. Due to severe symptoms of recurrent chest pain, faints and syncope, he eventually un-
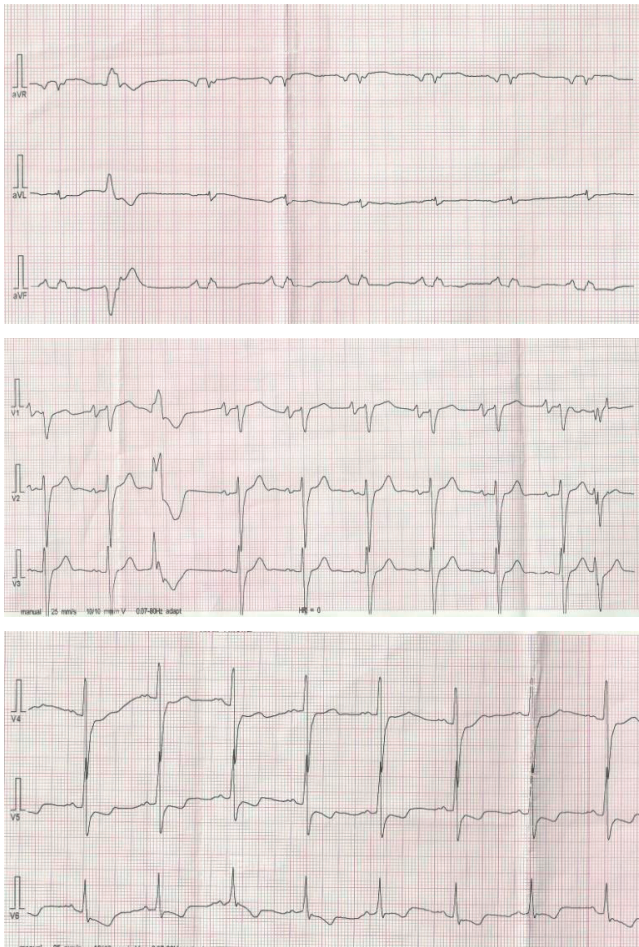
Figure 1. 12-leads electrocardiogram. Sinus rhythm, 75 beats per minute, indirect axis, double-phased of P waves in V1. Non-specific changes of ST-T segment

Figure 2. Transthoracic echocardiography. Apical four-chamber view. Dilated left ventricle and both atria. Relatively thin intraventricular septum with fibrosis of the basal segment of myocardium due to alcohol ablation (arrow). LV – left ventricle, LA – left atrium, RV – right ventricle, RA – right atrium

derwent successful alcohol septal ablation at the age of 35 years. Subsequently, for the next nine years he was almost asymptomatic and lived uneventful life. However, in few months preceding hospital admission, he started feeling gradual restlessness and increasing restriction of exercise tolerance. At the presentation he was in severe condition, in NYHA class IV, with shortness of breath at rest, peripheral oedemas, especially of lower extremities and required intravenous positive inotropic drugs including dopamine and dobutamine. His **basic biochemical parameters** were as follow: blood morphology revealed mild anaemia (Hb 13,2 d/dl, [normal range 14,0–18,0 g/dl]), liver transaminazes (Aspat 48 U/L [N <40] Alat 138 U/L [N<41] and GGTP 143 U/L [N <60] were slightly elevated, parameters of kidney functioning were within normal, C-reactive protein level was unremarkable above the norm (9,9 mg/L [N <5]), NT-pro BNP was significantly elevated to 4714 pg/ml [N<125]. The native protrombine index PT-INR was 1,94 (due to malfunction of liver [N 0,85–1,15]). Physical examination revealed regular heart rate of 75 beats per minute (bpm) blood pressure of 90/60 mmHg, on-air oxygen saturation of 97%. His respiratory rate was 15/min, on lungs auscultation, he was in Killip class 2.

12-leads ECG revealed sinus rhythm 75 bpm, indirect axis, double-phased of P waves in V1. Non-specific changes of ST-T segment.(Figure 1).

24-hour Holter-ECG registered sinus rhythm throughout with maximal HR 76 bpm, minimal 55 bpm and average HR 61 bpm, ventricular arrhythmias in the form of 4240 ventricular extrasystoles, one episode of ventricular tachycardia (VT) with HR 113 bpm – lasting 15 seconds and with 10 ventricular evolutions, supra-ventricular arrhythmias (3765), absence of circadian twenty–four–hour cycle.

An echocardiogram showed dilated LV (LV end-diastolic diameter – 71 mm; LV end-systolic diameter – 57 mm; LV end-diastolic volume –161 ml, LV end-systolic volume -142 ml) and both atrias (left atrial area 38 cm^2, right atrial area 39 cm^2), relatively thinned and hypocontractile intra-ventricular septum (Figure 2), severe global LV systolic dysfunction with ejection fraction of only 12%. Diastolic function was also significantly impaired and non-invasive estimation of LV filling pressure was grossly elevated (E/E' ratio of 20). Of note, features of pronounced pulmonary hypertension were observed with estimated systolic pressure in pulmonary artery (PASP) of 67 mm Hg. Additionally, severe, secondary tricuspid and moderate mitral regurgitation were observed (Figure 3). At sub-sternal projection wide (23 mm) and non-collapsing vena cava inferior (IVC) was seen.

X-ray of the chest showed picture of pulmonary stasis and presence of fluid in the left pleura.

After a few days of intensive therapy, including intravenous diuretics and inotropic positive drugs (dopamine and dobutamine), when the relative hemodynamic stabilization was achieved, the patient underwent objective assessment of functional status and invasive diagnostic tests.

In **cardiopulmonary exercise test** patient demonstrated evidently low tolerance of physical activity (peak load 5,4 METs) with peak oxygen consumption of only 14,8 ml/kg/min, representing 43% of referenced values for age and gender. Moreover, minute ventilation and carbon dioxide production (VE/VCO$_2$) ratio was also significantly elevated to 37,2 (normal values below 30). Anaerobic thresh-
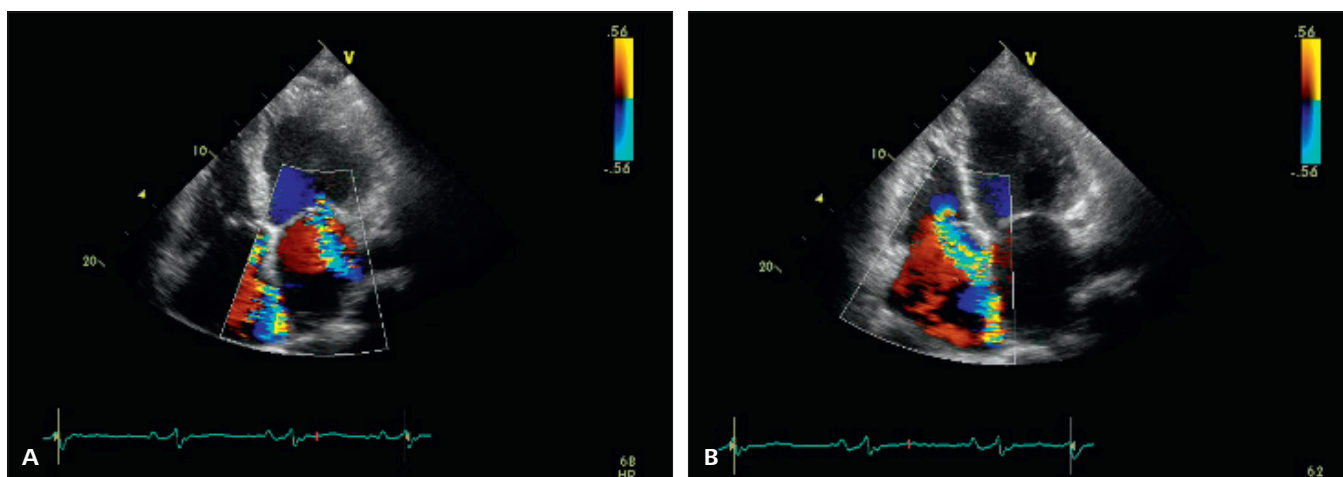
Figure 3. Transthoracic echocardiography. Apical four-chamber view. Colour Doppler imaging. Moderate mitral regurgitation (**A**) and severe, secondary tricuspid insufficiency (**B**)
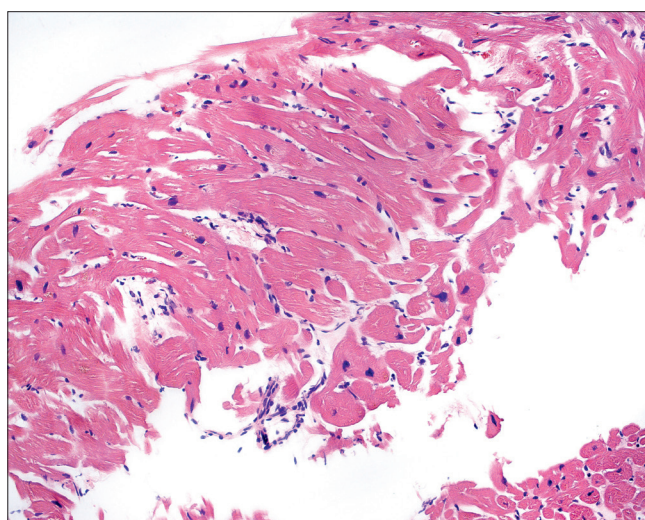
Figure 4. Histopathological study. Endiomyocardial biopsy sample. Hematoxylin eosin staining. Hypertrophy of cardiomyocytes. No signs of fibrosis or acute inflammatory infiltrations

old was obtained at the oxygen consumption of only 5,6 ml/kg/min which constitutes 16% of maximal predicted value.

Invasive studies – **coronarography and right heart catherization** have been also conducted. Angiography of epicardial coronary arteries did not reveal any significant stenoses or any other coronary anomalies. Of note, previously ablated septal branch was only fragmentally visible. Right heart catherization confirmed the presence of severe systolic dysfunction (cardiac output of 3 l/min and cardiac index of 1,6 l/min/m^2), and diastolic dysfunction (pulmonary capillary wedge pressure, was 27 mmHg). Postcapillary pulmonary hypertension was diagnosed (pulmonary artery pressure of 56/20/37 mm Hg and relatively low pulmonary vascular resistance of 231 ARU). There was no decrease of pressure value and total resistance during hemodynamic nitric oxide (NO) test in pulmonary artery (pulmonary artery pressure of 55/27/37 mm Hg, pulmonary vascular resistance of 238 ARU).

Endomyocardial biopsy from the right interventricular septum revealed hypertrophy of cardiomyocytes. There was no evidence of fibrosis or acute inflammatory infiltration (Figure 4).

Experimental therapy with sildenafil 20 mg three times daily was initiated in this patient.

The patient was readmitted to our hospital after three months to evaluate his clinical status and make the decision about further management. At presentation he was stable, in relatively good condition, nevertheless still in NYHA class III. He did not have any decompensations of heart failure that required hospitalization during the last three months. Physical examination revealed alveolar sound on lungs auscultation and no peripherial oedemas. There was a significant improvement in his biochemical parameters: NTpro-BNP 2333 pg/mL [previous value – 4714 pg/mL], normalization of liver parameters (ALAT 23 U/L[N<41]; ASPAT 27U/L [N<40]), INR 1,18 [N 0,85–1,15].

However, the echocardiogram showed persisting LV dilatation with LV end-diastolic diameter of 71 mm (similar to baseline examination), severe global LV systolic dysfunction with ejection fraction of only 15%, impaired diastolic function (E/E' ratio of 19,6). Of note, features of pronounced pulmonary hypertension were still observed with PASP of 75 mm Hg. Based on the non-invasive estimation there is no decrease of pulmonary hypertension after 3-month sildenafil therapy. Nevertheless, on cardiopulmonary exercise test patient demonstrated significant improvement of physical tolerance (peak load 7,4 METs) with peak oxygen consumption of 18,4 ml/kg/min, representing 54% of referenced values for age and gender. Also right heart catherization revealed slightly improved hemodynamic parameters, especially reduction of pulmonary artery pressure to 43/21/29 mm Hg. Nevertheless patient still had severe systolic dysfunction (cardiac output of only 3 l/min and cardiac index of 1,6 l/min/m^2).

Taking into consideration the patient's clinical status and the results of additional examinations the decision about continuation of sildenafil therapy has been made. Patient reports better health status and denies qualification for the heart transplantation.

Discussion

In a comprehensive approach to this patient we included patient's symptoms, physical examination and results of additional studies such as electrocardiogram, echocardiogram, laboratory findings, Holter-ECG, invasive procedures: coronarography, right catherization, and microscopic findings. Based on clinical findings and data from conducted examinations our patient was diagnosed with dilated end-stage phase of HCM. After a few days of intensive, intravenous therapy and achieving hemodynamic stabilization, patient's therapy was optimized with guideline-approved heart failure medications of oral drugs including loop diuretic, beta-blocker, angiotensin converting enzyme inhibitor and mineralocorticoid antagonist. Additionally, he was also started with off-label sildenafil with an aim for the reduction of significant pulmonary hypertension.

Based on the literature and an experience the clinical efficacy of alcohol septal ablation for HCM is good in terms of symptoms relief but it's long-term effect remains uncertain [6]. Our patient underwent alcohol ablation of basal segment of interventricular septum due to symptoms resulting from LVOT obstruction. After effective procedure he exhibited only mild residual gradient and he had definitely better comfort of his daily life. This favourable status was maintained for the next few years, and therefore patient remained under only occasional cardiological follow-up and there is no set time-point when actually his LV started to dilate.

End-stage HCM, the stadium in which our patient was admitted to the hospital, is also characterized with higher incidence of ventricular arrhythmias and poor prognosis [7]. Of note, patients with end-stage HCM are more often male. Presence of sustained or non-sustained ventricular tachycardia (VT) constitutes the major indication for the qualification to cardioverter-defibrillator implantation (ICD) as a primary prevention of sudden cardiac death (SCD). Our patient had ventricular arrhythmias with an episode of non-sustained VT registered during the Holter monitoring ECG and therefore he was qualified for ICD. Perhaps, if he had had ECG evidence of electrical dyssynchrony (wide and disturbed QRS), he should have been probably qualified also for cardiac resynchronization therapy (CRT) as it was proved to have a good effect on heart failure symptoms and can slow or even reverse LV remodeling [9]. However, our patient's QRS duration was only 110 ms without typical left bundle branch block morphology and as a result he was not a "classic" candidate for CRT.

One of the paramount problem of concern in end-stage HCM patients is the progressive SHF. Progressive SHF, regardless of its pathomechanisms [10,11], leads to the gradual worsening of the disease and eventually to death due to pump-failure. Therefore, appropriate timing for heart transplantation (HTX) and/or ventricular assists devices (VADs) is crucial. However, severe and non-reversible secondary pulmonary hypertension, which is the result of an advanced LV systolic and diastolic dysfunction, is a classic contraindication for HTX [12]. Such a secondary pulmonary hypertension might have probably caused acute right ventricle insufficiency of newly-transplanted heart, which would dramatically increase the incidence of premature mortality in perioperative period [13,14]. The patient, discussed in this case report, had moderate secondary, venous pulmonary hypertension with relatively low pulmonary vascular resistance (<2,9 Wood units). Additionally, there was no decrease of pulmonary pressure after nitric oxide reversibility test. However, according to the literature, long term duration of sildenafil administration causes reduction of pulmonary hypertension [15]. Therefore the patient was started with sildenafil and he is planned for controlled right catherization after 3 months of therapy and then consider evaluation to heart transplantation.

References

1. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013; 381: 242–255.

2. Bos JM, Towbin JA, Ackerman MJ. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 201–211.

3. Hughes SE. The pathology of hypertrophic cardiomyopathy. Histopathology 2004; 44: 412–427.

4. Goto D, Kinugawa S, Hamaguchi S, et al. Clinical characteristics and outcomes of dilated phase of hypertrophic cardiomyopathy: report from the registry data in Japan. J Cardiol. 2013; 61: 65–70.

5. Thaman R, Gimeno JR, Murphy RT et al. Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. Heart 2005; 91: 920–925.

6. Sorajja P, Ommen SR, Holmes DR Jr, et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2012; 126: 2374–2380.

7. Hamada T, Kubo T, Kitaoka H et al. Clinical features of the dilated phase of hypertrophic cardiomyopathy in comparison with those of dilated cardiomyopathy. ClinCardiol. 2010; 33: E24–E28.

8. Harris KM, Spirito P, Maron MS et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation 2006; 114: 216–225.

9. Rogers DP, Marazia S, Chow AW et al. Effect of biventricular pacing on symptoms and cardiac remodelling in patients with end-stage hypertrophic cardiomyopathy. Eur J HeartFail. 2008; 10: 507–513.

10. Maron BJ, Towbin JA, Thiene G et al. American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies. Circulation 2006; 113: 1807–1816.

11. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002; 287: 1308–1320.

12. Costanzo MR, Augustine S, Bourge R et al. Selectionand Treatment of Candidates for Heart Transplantation: A Statement for Health Professionals From the Committeeon Heart Failure and Cardiac Transplantation of theCouncil on Clinical Cardiology, American Heart Association [AHA Medical/Scientific Statement]. Circulation 1995; 92: 3593–3612.

13. Bourge RC, Kirklin JK et al. Analysis and predictors of pulmonary vascular resistance after cardiac transplantation. J Thorac Cardiovasc Surg 1991; 101: 432–444.

14. Espinoza C, Manito N, Castells E et al. Reversibility of pulmonary hypertension in patients evaluated for orthotopic heart transplantation; importance in postoperative morbidity and mortality. Transplant. Proc. 1999; 31: 2503–2504.

15. Nowacka M, Kopec G, Stepniewski J, Podolec P. Nitric oxide vs Sildenafil for pulmonary artery reactivity testing in heart trans plantation candidates. J Rare Cardiovasc Dis 2012; 1: 7–9.