Noninvasive assessment of intramyocardial coronary flow in hypertrophic cardiomyopathy by high-resolution Doppler echocardiography

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Dyspnea and angina have been described in patients with hypertrophic cardiomyopathy (HCM). Given the complexity of the coronary microcirculation, the pathophysiological mechanisms of angina are discussed.

The last generation of echo devices allows the investigation of epicardial coronary flow by means of the standard transthoracic approach (TTE).

In the present study we describe 5 patients affected by HCM (with outflow tract dynamic obstruction in 2 cases, intraventricular dynamic obstruction in the other 2, no obstruction in the last one) in whom both the epicardial and intramyocardial coronary flows were assessed at high-resolution TTE.

Regular flow velocities were shown in epicardial coronary arteries, while in intramyocardial branches the diastolic peak velocity was > 75 cm/s in all patients. Besides, the systolic flow was found to be inverted.

Similar to what suggested by the few data presently available in the literature, the main findings of this study confirm the appropriateness of investigating the intramyocardial coronary circulation in patients with HCM by means of high-resolution Doppler echocardiography. In order to explain this clinical finding, an interesting hypothesis of a diastolic "milking-like" phenomenon associated with systolic "blood squeezing" in the intramural coronary arteries was taken into consideration. The noninvasive study of the intramyocardial coronary flow may be clinically relevant even in the evaluation of the effectiveness of the adopted therapeutic strategy in reducing myocardial wall stress in severe ventricular hypertrophy.

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Introduction

Hypertrophic cardiomyopathy (HCM) is a primary cardiac disease due to a variety of mutations in the gene encoding the sarcomeric proteins. The phenotypes are characterized by an increased left ventricular mass without chamber dilation[1,2]. The quantitative assessment of hypertrophy, including tissue characterization, wall motion, ventricular function and related modifications have been well investigated by means of transthoracic echocardiography (TTE)[2,3].

Both angina and dyspnea are usual symptoms in patients with HCM. Besides, the different pathophysiological mechanisms, above all the discrepancy between the coronary bed and the left ventricular mass, have been discussed[4-8].

In the last few years the technological improvements in noninvasive ultrasound devices have permitted cardiologists to investigate coronary flow modifications in real time. In fact, the determination of the coronary flow reserve, contrast imaging and intravascular ultrasound are, together with those obtainable by means of other invasive methods, important parameters to be borne in mind if one is to obtain relevant information on the left anterior descending coronary artery (LAD) flow and tissue perfusion[8-12].

Patients with HCM were found to have, compared to controls, a higher diastolic velocity in the LAD and hence a reduced coronary flow reserve[11-13]. Unfortunately, only a few data about the noninvasive investigation of the intramyocardial coronary artery are presently available in the literature[14,15]. We present 5 patients with HCM in whom both the LAD and the intramyocardial coronary arteries were evaluated at high-resolution TTE.

Description of cases

Five Caucasian patients (4 males, 1 female, mean age 61.0 ± 15.2 years) presenting with HCM underwent clinical evaluation for recurrent palpitations and chest pain (first 4 patients only).

Patients A and E had a history of mild-to-moderate hypertension and were on ACE-inhibitor (trandolapril 5 mg and enalapril 20 mg daily respectively) treatment. Since there was no evidence of any specific etiology for left ventricular hypertrophy, the other 3 patients (B, C and D) were classified as having a primitive form in accordance with the criteria of Wigle et al.[16] and hence received verapamil (120 to 360 mg daily).

Within the 12 months prior to admission, patients A, B and D had been submitted to an exercise stress ECG but no significant signs of acute ischemia were demonstrated. Patients C and E were not submitted to this test because of the presence of severe left ventricular dynamic obstruction.

On admission, resting ECG showed normal sinus rhythm, high R-wave voltages and widespread ventricular repolarization abnormalities in all patients, an atrioventricular conduction delay (PR duration 240 ms) in patient E and an isolated left anterior fascicular block in patients A and C which was associated with right bundle branch block in patient D.

All patients underwent TTE which was performed using an Acuson Sequoia unit (Siemens Company, Mountain View, CA, USA) equipped with multifrequency phased array transducers, harmonic imaging software (2.0/4.0 MHz transmit/receive frequency with conventional probe, 3.5/7.0 MHz with high-frequency probe). The standard long- and short-axis apical 2-, 4- and 5-chamber and additional off-axis sections were considered for examination. The Nyquist limit, pulse repetition frequency and spectrum filters were adjusted to detect low flow velocities (range 10-70 cm/s) and to minimize tissue interference.

The absolute left ventricular mass and two-dimensional left ventricular ejection fraction were calculated according to the Penn convention[17] and the American Society of Echocardiography recommendations[18] respectively.

Color and power-coded Doppler echocardiography were used in order to determine the LAD and intramyocardial coronary flows. The coronary flow velocities were measured by means of pulsed-wave Doppler sampling with a conventional (4 MHz) or high (7 MHz) frequency transducer. Anyway, no significant difference between the methods was observed in obtaining the best spectrum signal. No contrast agents were used in the study.

Clinical data and echocardiographic findings are shown in table I. The main typology of left ventricular hypertrophy was morphologically symmetrical in 3/5 patients (2 of whom had apical and mid-ventricular dynamic obstruction respectively) and asymmetric in the other 2, who presented with severe outflow tract dynamic obstruction. A regular flow velocity in the distal segments of the LAD was found in all patients (Table I).

When compared with the normal range limit reported by Minagoe et al.[14,15], higher forward (from the epicardial to the endocardial edge) diastolic velocities were disclosed in each intramyocardial coronary artery (Table I, Figs. 1-4). In these vessels, notwithstanding the different peak velocities and diastolic slopes, a Doppler pattern with a similar morphology was demonstrated. In ad-

Table I. General data and main echocardiographic findings.

	Patient A	Patient B	Patient C	Patient D	Patient E
Sex	M	M	F	M	M
Age (years)	67	79	64	62	33
Blood pressure (mmHg)	160/80	140/70	135/80	135/70	170/80
Heart rate (b/min)	74	64	57	65	59
LV diastolic diameter (mm)	46	48	55	51	56
LV systolic diameter (mm)	28	32	35	31	34
IVS diastolic thickness (mm)	16	15	21	14	22
PW diastolic thickness (mm)	15	14	8	12	14
Apical wall thickness (mm)	18	18	17	19	18
LV ejection fraction (%)	74	79	67	68	70
LV mass (g)	341.7	346.2	439.4	323.2	613.6
LVH typology	Symmetric	Symmetric	Asymmetric	Symmetric	Asymmetric
LVH predominant distribution	Mid-apical	Apical	Septal	Mid-ventricular	Septal
Mitral valve E/A ratio	0.90	0.80	0.65	0.74	2.2
E-wave deceleration time (ms)	164	193	158	165	207
Mid-ventricular PG (mmHg)	30 (S)	0	0	38 (D)	0
LV outflow resting PG (mmHg)	40	26	150	25	140
Epicardial LAD systolic velocity (cm/s)	15	18	20	26	28
Epicardial LAD diastolic velocity (cm/s)	45	36	45	42	48
IMCA peak diastolic velocity (cm/s)	109.7	77.6	143.9	154.9	137.2
IMCA mean diastolic velocity (cm/s)	94.2	58.3	103.5	108.1	89.5
IMCA flow systolic inversion	+	?	+	+	+

D = diastolic; E/A = early/late diastolic mitral velocity ratio; IMCA = intramyocardial coronary artery; IVS = interventricular septum; LAD = left anterior descending coronary artery; LV = left ventricular; LVH = left ventricular hypertrophy; PG = peak gradient; PW = posterior wall; S = systolic.

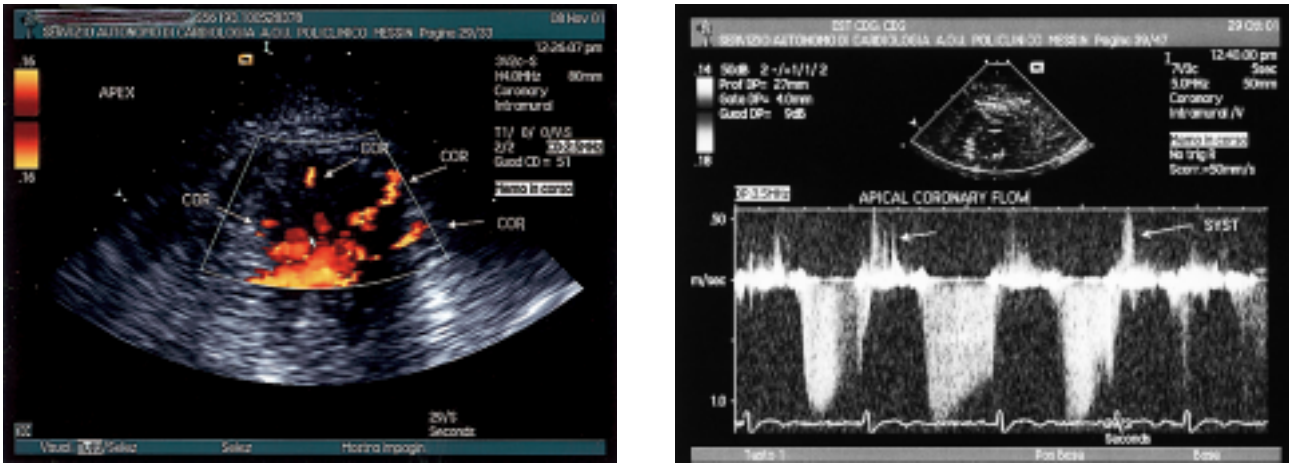

Figure 1. *Apical 4-chamber view* (left panel) *in patient A (mid-apical hypertrophy). Four small intramural coronary branches may be seen at power-Doppler echocardiography. The pulsed-wave Doppler velocity sampling refers to the largest branch* (right panel). *The diastolic velocity, from the epicardial to the endocardial edge, is > 100 cm/s, while the systolic flow appears to be reverted* (arrows). *Two-dimensional image settings: transducer frequency 4 MHz; depth 80 mm; power spectrum range 16 cm/s; gain 51 dB. COR = intramural coronary branches; SYST = systolic flow velocity.*

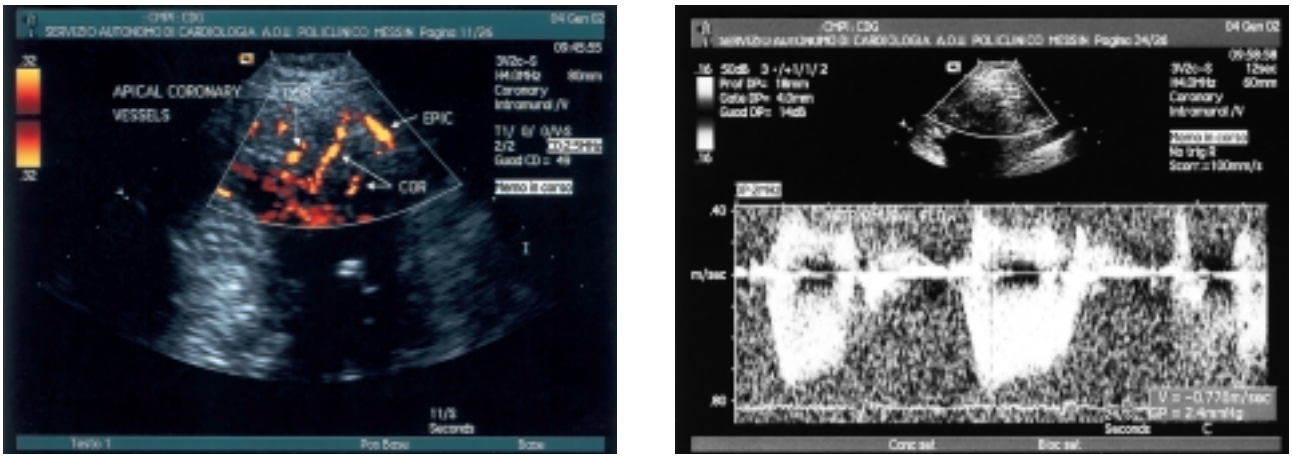

Figure 2. *Modified apical 4-chamber view* (left panel) *in patient B. The distal segment of the epicardial left anterior descending coronary artery and the small intramyocardial coronary artery branches are displayed* (arrows). *At pulsed-wave Doppler, the diastolic peak velocity (77.6 cm/s) was observed in the largest branch* (right panel). *No adequate systolic signal is available in this frame. This was also due to the presence of interference by the native epicardial left anterior descending coronary artery signal. Two-dimensional image settings: transducer frequency 4 MHz; depth 80 mm; power spectrum range 32 cm/s; gain 49 dB. COR = intramural coronary branches; EPIC = epicardial coronary artery.*

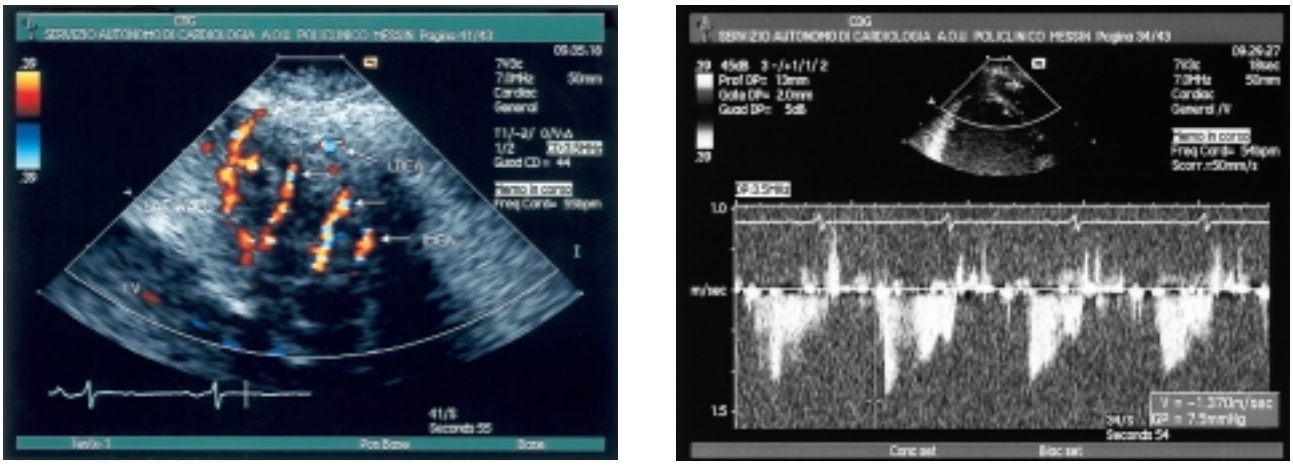

Figure 3. *Modified apical 4-chamber view, with magnification of the lateral wall* (left panel) *in patient E. In this frame, the intramyocardial coronary artery (IMCA) flow was assessed by means of a high-frequency transducer and standard color Doppler analysis. The diastolic peak velocity reaches 137 cm/s and the systolic component is inverted. It is noteworthy that the atrial systolic contribution seems to modify the coronary diastolic slope* (right panel). *Two-dimensional image settings: transducer frequency 7 MHz; depth 50 mm; velocity range 39 cm/s; gain 44 dB. LDCA = left anterior descending coronary artery; LV = left ventricle.*

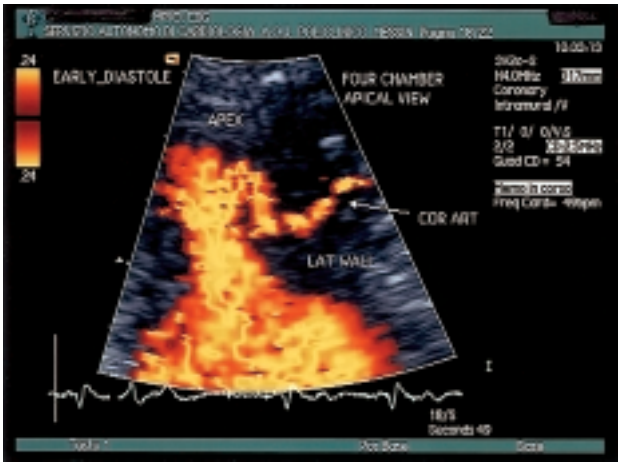

Figure 4. *Magnified imaging of the apical region in patient D (hypertrophic cardiomyopathy with mid-ventricular diastolic obstruction). Power Doppler echocardiography reveals the presence of an intramyocardial coronary artery branch. Interestingly, a mid-ventricular size reduction starting in early-diastole can be noted. Two-dimensional image settings: transducer frequency 4 MHz; depth 17 mm; power spectrum range 24 cm/s; gain 54 dB.*

dition, it is noteworthy that the diastolic flow velocity seemed to be modified even by the atrial contraction, as shown in patient E (Fig. 3, right panel).

A reverted short-lasting widespread systolic signal was observed in 4/5 patients. In the other patient, the native epicardial LAD signal interfered with the intramyocardial coronary artery systolic spectrum (Fig. 2, right panel).

Discussion

The recurrence of angina in patients with HCM may be evoked by different mechanisms. Apart from the presence of coronary atherosclerosis, a reduced coronary flow reserve in the epicardial branches, consequent to inadequate vasodilation and increased oxygen consumption, has been already demonstrated[10-12]. More recently, the association between an impaired coronary flow reserve and left ventricular hypertrophy in hypertensive patients free of coronary artery stenosis was also confirmed[19].

In patients with HCM, histological findings at necropsy demonstrated the presence of an abnormal intramural vascular structure consistent with wall thickening and a decreased vessel size. Also for these reasons, such mechanisms as "small vessel disease" whether associated with vasospasm has already been evaluated[6,7,20].

In view of their excellent time-spatial resolution, presently available new echo devices allow the evaluation of several segments of the LAD in many patients[8,10,14,15]. The diastolic peak velocity in these vessels has been reported to be higher in patients with HCM than in healthy subjects in whom the upper limit does not usually exceed 50 cm/s[10,12-15].

To date, only very few data concerning the visualization of the intramyocardial coronary flow have been published. Minagoe et al.[14] have reported a feasibility of 88% in patients with HCM and of 61% in controls. In their population the mean diastolic peak velocity was 77 ± 36 cm/s in the first group and 31 ± 10 cm/s in controls[14,15].

Basically, we can confirm the practical appropriateness of assessing the intramyocardial coronary flow in patients with HCM using precordial high-resolution Doppler echocardiography. In our population, the diastolic peak velocities were significantly higher than the normal range limit suggested by the above-mentioned studies[14,15]. Similarly, we also confirm the reversal in the coronary systolic flow.

The mechanism underlying these findings has not yet been established. The already described "coronary milking" phenomenon due to myocardial bridging[21,22] may be taken into account to explain the high diastolic velocity in the intramyocardial coronary artery. However, in view of the demonstration of coronary artery wall thickening in HCM, we cannot exclude the existence of a chronic abnormal parietal relaxation even as a consequence of the high left ventricular diastolic pressure. The myocardial bridging, which was essentially recognized in epicardial arteries at angiography, appears not to be easily established by TTE.

On these grounds, the presence of advanced left ventricular diastolic dysfunction, indirectly expressed by a pseudo-normalized E/A ratio or a restrictive pattern, might be taken into account when predicting coronary microcirculatory impairment. However, no data supporting the latter hypothesis have been provided by recent studies in the absence of LAD atherosclerosis.

The question arises whether the systolic flow inversion might depend on a "blood-squeezing" mechanism. In fact, both flow inversion and signal spreading could be interestingly related to the rapid myocardial pressure rise, otherwise common in patients with HCM. In order to confirm this suspicion, it should be considered that the intramural pressure gradient from the endocardial to the epicardial edge in the hypertrophic wall is significantly higher than in a cardiac wall with a normal thickness[2].

In our experience, the use of high-frequency transducers (5 MHz for anatomical imaging and 7 MHz for color Doppler assessment) improves the visualization of the intramyocardial coronary flow but can also be responsible for more extra-tissue interference than standard transducers. Besides, such a "radial" just as much as complex disposition of the intramural coronary arteries emerged in almost the whole population. In fact, when an adequate acoustic window is available, transverse and longitudinal intramural microvessels can be seen using high-frequency transducers.

The main limitation of the present study is the small number of patients. However, despite its fascinating feasibility, the method is time-consuming and sometimes provides no adequate pulsed-wave Doppler curves for velocity quantification (see patient B). The latter bias is essentially due both to the small vessel diameter as well

as to the heart systolic translation that hinder correct alignment of the Doppler sample volume with the flow direction.

Given the limited number of publications in this field, even scant information on the new method may contribute to improve knowledge about the noninvasive assessment of the myocardial microcirculation in HCM. The lack of a control group likely represents another study bias. However, our experience has shown that in case of a myocardium with normal thickness, the method was routinely inadequate for the precise evaluation of intramyocardial coronary flow if contrast agents were not resorted to. It was also for this reason that we decided to compare our findings to already available data referring to normal subjects.

A comparison with other invasive methods (Doppler flow-wire, quantitative angiography, magnetic resonance) might provide, through a different perspective, complementary information on the pathophysiology of these findings.

In the light of aforementioned features, the main findings of the present study lend further support to the proposal of assessing the intramural coronary circulation in HCM by means of TTE. A diastolic "milking-like" mechanism in the intramyocardial coronary artery, especially in patients showing high intraventricular pressure gradients, has been hypothesized.

While the role of left ventricular diastolic dysfunction is discussed, a systolic "blood squeezing" phenomenon was disclosed in almost the whole population examined.

Future larger studies should be addressed towards the standardization of the method, in view of the growing interest in its clinical use for the evaluation of the effectiveness of the adopted therapeutic strategy in decreasing myocardial wall stress in patients with severe left ventricular hypertrophy.

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References

1. Shaver JA. Cardiomyopathies: clinical presentation, differential diagnosis and management. Philadelphia, PA: FA Davis, 1988.
2. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002; 287: 1308-20.
3. Levy D, Savage DD, Garrison RJ, et al. Echocardiographic criteria for left ventricular hypertrophy: the Framingham study. Am J Cardiol 1987; 59: 956-60.
4. Shah PM. Newer concepts in hypertrophic obstructive cardiomyopathy. JAMA 1979; 242: 1771-6.
5. Spirito P, Maron BJ, Bonow RO, et al. Severe functional limitation in patients with hypertrophic cardiomyopathy and only mild localized left ventricular hypertrophy. J Am Coll Cardiol 1986; 8: 537-44.
6. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986; 8: 545-57.
7. Stewart S, Schreiner B. Coexisting idiopathic hypertrophic subaortic stenosis and coronary artery disease: clinical implication and operative management. J Thorac Cardiovasc Surg 1981; 82: 278-80.
8. Caiati C, Montaldo C, Zedda N, et al. A new non-invasive method for coronary flow reserve assessment: contrast-enhanced transthoracic second harmonic echo Doppler. Circulation 1999; 99: 771-8.
9. Sgura FA, Di Maio C. Intravascular ultrasound in clinical practice. Ital Heart J Suppl 2001; 2: 579-92.
10. Iliceto S, Memmola C, Rizzon P. Coronary reserve assessed by transesophageal Doppler echocardiography in patients with hypertrophic cardiomyopathy. In: Dagianti A, Feigenbaum H, eds. Echocardiography 1993. Amsterdam: Elsevier Science, 1993: 407-8.
11. Tries HP, Lethen H, Lambertz H. Coronary flow reserve: a practical echocardiographic approach. Hounslow: Siemens House, 2001.
12. Hozumi T, Yoshida K, Akasaka T, et al. Noninvasive assessment of coronary flow velocity and coronary flow velocity reserve in the left anterior descending coronary artery by Doppler echocardiography: comparison with invasive technique. J Am Coll Cardiol 1998; 32: 1251-9.
13. Asami Y, Yoshida K, Hozumi T, et al. Assessment of coronary flow reserve in patients with hypertrophic cardiomyopathy using transthoracic color-Doppler echocardiography. J Cardiol 1998; 32: 247-52.
14. Minagoe S, Toyama Y, Niizoe K, et al. Transthoracic Doppler echocardiographic detection of intramyocardial coronary artery flow in humans using high frequency transducers. J Cardiol 1997; 30: 149-55.
15. Minagoe S. Transthoracic Doppler echocardiographic assessment of left anterior descending coronary artery and intramyocardial small coronary artery flow in patients with hypertrophic cardiomyopathy. J Cardiol 2001; 37 (Suppl 1): 115-20.
16. Wigle ED, Kitching AD, Rakowski H. Cardiomiopatia ipertrofica. In: Braunwald E, ed. Atlante delle malattie cardiache. Cardiomiopatie, miocarditi e malattie del pericardio. Vol 2. London: Science Press, 1997: 1-22.
17. Devereux RB, Reicheck N. Echocardiographic determination of the left ventricular mass: anatomic validation of the method. Circulation 1997; 55: 613-8.
18. American Society of Echocardiography Committee on standards, subcommittee on quantitation of two-dimensional echocardiograms: recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989; 2: 361-7.
19. Galderisi M, Cicala S, De Simone L, et al. Impact of myocardial diastolic dysfunction on coronary flow reserve in hypertensive patients with left ventricular hypertrophy. Ital Heart J 2001; 2: 677-84.
20. Dimitrow PP. Coronary vasospasm in hypertrophic cardiomyopathy. Chest 2001; 119: 1289-91.
21. Yetman AT, MacDonald C, McCrindle BW, et al. Myocardial bridging with coronary compression in children with hypertrophic cardiomyopathy: a risk factor for sudden death. N Engl J Med 1998; 339: 2101-9.
22. Alfonso F, McKenna WJ. Milking in hypertrophic cardiomyopathy. J Am Coll Cardiol 1999; 34: 949-50.