A case of hypereosinophilic cardiomyopathy: additional value of the myocardial contrast agent SonoVue for the differential diagnosis of a cardiac mass

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We describe the case of a 37-year-old male referred because of hypereosinophilia associated with dyspnea. Transthoracic harmonic echocardiography showed an extensive myocardial infiltration and highlighted an intraventricular "in plus" image, whose characteristics were compatible with a diagnosis of intracardiac thrombus. The use of the myocardial contrast agent SonoVue (1 ml in bolus i.v. and 4 ml at an infusion velocity of 2 ml/min) allowed us to immediately identify, during left ventricular chamber opacification, the exact endocardial border of the left ventricular cavity and, later (when the residual SonoVue was evident only at the level of the myocardial walls), the true characteristics of the "in plus" image. This approach revealed the infiltration of the myocardial tissue and of both papillary muscles and chordae tendinae. The use of the myocardial contrast agent SonoVue may be, therefore, useful to distinguish the origin of "in plus" images often evident at echocardiography in the hypereosinophilic syndrome.

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Introduction

The hypereosinophilic syndrome represents a heterogeneous group of hematologic disorders characterized by an excessive production of eosinophils. A major cause of the morbidity and mortality associated with this syndrome is attributable to the cardiac involvement[1]. Several studies focused on the echocardiographic evaluation of the cardiac abnormalities associated with this pathology, in particular eosinophilic infiltration and endomyocardial fibrosis[2-8]. Congestive heart failure may result from endomyocardial fibrosis[9-11] and from valve alterations, both secondary to eosinophilic infiltration[12]. In this syndrome the occurrence of thromboembolic episodes is frequent[13]. In this report, we present the echocardiographic findings of a patient with a hypereosinophilic syndrome showing an "in plus" image in the left ventricular (LV) internal chamber which was suggestive of thrombus formation.

Case report

A 37-year-old male was referred to our echocardiographic laboratory from the Division of Hematology where a diagnosis of hypereosinophilic syndrome had been made. The patient referred both effort and resting dyspnea during the last month. Hematological evaluation showed: white blood cell count 23 000/mm^3 (neutrophils 27%, eosinophils 58%), hemoglobin 12.3 g/dl, mean corpuscular volume 86 fl, platelets 54 000/mm^3. Bone marrow cytology showed eosinophilic dysplasia (ring eosinophils) with signs of dysgranulopoiesis.

At the time of our observation, the patient's hemodynamic status was normal, with a blood pressure of 110/85 mmHg. His heart rate was 88 b/min. Cardiac objective examination revealed a cardiac area within the normal limits, an apical grade II-III/IV systolic murmur and a basal protodiastolic murmur. ECG signs of LV hypertrophy ($S_{V3} + R_{aVL}$ 25 mm) and of LV systolic overload as well as abnormalities of repolarization were evident at resting ECG.

The patient was submitted to transthoracic harmonic echocardiography using a Vingmed System Five (GE, Horten, Norway) with a 2.5 MHz transducer. M-mode quantitative analysis showed LV eccentric hypertrophy (LV mass index 53.2 g/m$^{2.7}$,

relative wall thickness 0.32). The LV ejection fraction was 69%. Two-dimensional echocardiography in the parasternal views, in particular the short-axis view, showed evidence of multiple, small echo-redundant "in plus" images in the LV internal chamber, close to the interventricular septum and to the posterior wall, whose motion was synchronous with the phases of the cardiac cycle (Fig. 1). The apical views revealed an extensive "in plus" image, adherent to the LV myocardial walls and involving the apical region, mildly separated from the myocardium and with free pedunculated parts lying in the LV chamber (Fig. 2). Mild to moderate mitral regurgitation and mild pulmonary valve insufficiency were detected at Doppler interrogation. Standard Doppler mitral inflow allowed to recognize an E/A ratio of 2.0, with an E peak velocity of 0.85 m/s and an E wave deceleration time of 154 ms, while the myocardial E velocity of tissue Doppler-derived LV mitral annulus (Ea) was 0.11 cm/s, thus resulting in an E/Ea ratio of 7.8 (Fig. 3).

An i.v. infusion of the myocardial contrast agent SonoVue (Bracco SpA, Milan, Italy) was used according to the standard protocol[14]. Five ml were administered (1 ml in fast bolus and 4 ml at an infusion velocity of 2 ml/min), constantly utilizing harmonic capabilities but without the aid of a dedicated software for myocardial contrast echocardiography. Immediately after the infusion, the infiltrated LV (end-diastolic and end-systolic) endocardial borders could be optimally evaluated while this technique did not provide any additional information regarding the demarcation between the myocardial walls and internal chamber structures. During the subsequent minutes (about 12 min after the end of the infusion), when the SonoVue had disappeared from the internal cavity and persisted only at the level of the myocardium, it was possible to optimally assess the "in plus" image (Fig. 4). The structure, previously believed to be an intracardiac mass associated with pedunculated formations, appeared to form part of the thick myocardial infiltration involving both papillary muscles and the chordae tendinae and was characterized by its marked echo-density and large dimensions. In particular, because of the eosinophilic infiltration magnified by SonoVue, almost the entire course of the

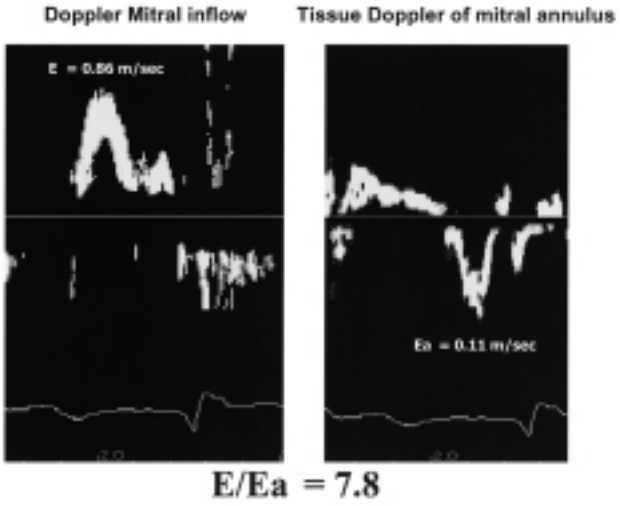

Figure 3. *Standard Doppler inflow* (left panel) *and tissue Doppler of the left ventricular mitral annulus* (right panel). *The E/Ea ratio is 7.8.*

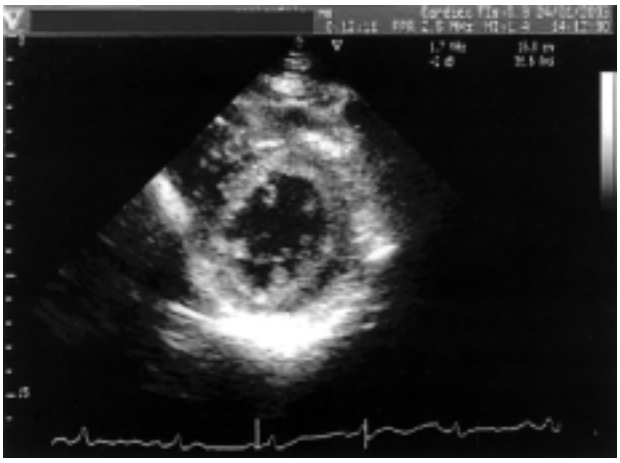

Figure 1. *Tissue harmonic two-dimensional echocardiography. A parasternal short-axis view of the left ventricle shows multiple, echo-redundant filaments in the chamber, contiguous with the interventricular septum and the inferior and posterior walls.*

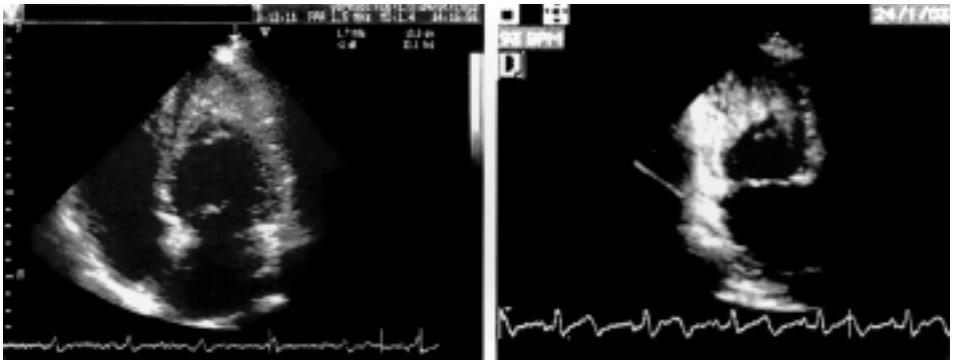

Figure 2. *Tissue harmonic apical 4-chamber* (left panel) *and 2-chamber* (right panel) *views: an "in plus" image, suggestive of the presence of extensive endomyocardial eosinophilic infiltration, is evident in the left ventricular chamber at the level of the apical region.*

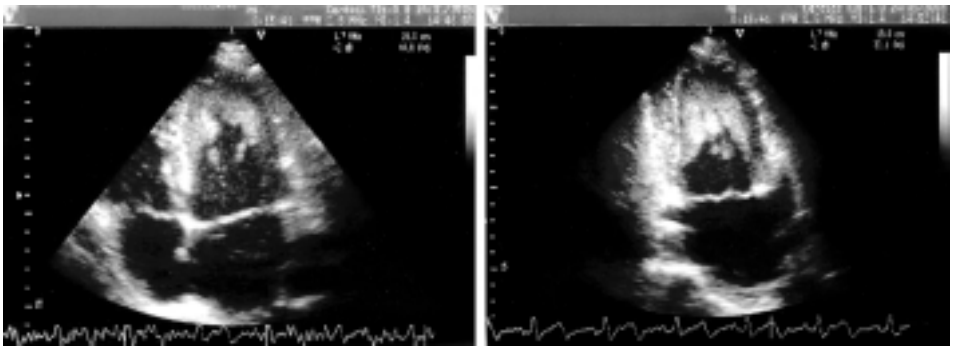

Figure 4. *Tissue harmonic apical 4-chamber* (left panel) *and 2-chamber* (right panel) *views 12 min after the end of SonoVue i.v. infusion. It may be seen that the endomyocardial infiltration involves not only the left ventricular walls but also the papillary muscles and the chordae tendinae. The postero-medial muscle* (on the left) *and the antero-lateral papillary muscle* (on the right) *together with their respective chordae are identifiable in the 4-chamber view. In the 2-chamber view the image of the postero-medial papillary muscle may be seen to lie between the anterior and inferior walls and both the infiltrated chordae are clearly visible.*

chords was visible both in the 4-chamber and 2-chamber views.

The patient was placed on anticoagulant dicoumarol treatment, in relation to the elevated thromboembolic risk characteristic of the hypereosinophilic syndrome.

Discussion

This case report highlights one of the possible applications of myocardial contrast agents in echocardiography. Their appropriate use represents an additional tool for optimal LV chamber volume determination and/or for myocardial wall perfusion but also for a more accurate differential diagnosis in some clinical conditions in which standard imaging is difficult to interpret. In the specific case, the clear definition of the wall infiltration was essential to understand the nature of the "in plus" image of the LV chamber.

The subendocardial infiltration detected in the present case report is typical of the infiltrative cardiomyopathy associated with hypereosinophilia, referred to in the scientific literature as fibroplastic endomyocarditis or Loeffler's syndrome. Its clinical picture is usually characterized by aspecific symptoms such as dyspnea, chest pain, syncopal episodes and cardiac rhythm abnormalities. This syndrome is characterized by the eosinophilic infiltration of numerous organs including the heart, particularly the subendocardial regions[1-13]. In this syndrome, the formation of cardiac thrombi in the LV internal chamber is not infrequent, due to the adhesion of platelets and other corpuscular elements[13]. The majority of thrombi are intramural, above all in the apical region, and may extend to the LV outflow tract. The presence of a thrombus is often associated with secondary mitral regurgitation[12] and with a LV filling pattern consistent with a restrictive physiology[13,15,16]. Considering the above, one may easily understand why Loeffler's syndrome may induce LV failure[9,13,16]. In our case, however, the combined analysis of standard Doppler and tissue Doppler-derived patterns of the LV mitral annulus showed an E/Ea ratio of 7.8, thus suggesting a normal filling pattern. An E/Ea ratio < 11 is very sensitive in excluding the presence of a restrictive or pseudonormal pattern[17]. Of note, pulsed tissue Doppler is relatively preload-independent and the American Society of Echocardiography encourages its use for the differential diagnosis between a normal and a pseudonormal/restrictive LV mitral pattern[18].

In our case report, the diagnosis of endomyocardial infiltration, typical of Loeffler's syndrome, was made at transthoracic echocardiography. Typically, the eosinophilic wall infiltration accentuates the echocardiographic reflection and makes the myocardial tissue thicker than in normal conditions and much more clearly definable than the contiguous pericardium. The doubt which arose during the examination regarded the nature of what appeared as an "in plus" image in the LV internal chamber, specifically in the apical region. The therapeutic implications of this differential diagnosis are crucial for the choice of the adequate anticoagulant therapy. Worthy of note, the occurrence of cardiac thrombi has been reported to have a prevalence of about 50% in this disease[13]. In view of our finding, it is conceivable that this figure is an overestimation, since cases in which the papillary muscles and chordae tendinae are involved may be misdiagnosed when transthoracic echocardiography is performed without the use of myocardial contrast agent.

Indeed, the use of SonoVue allowed us to better define the infiltrated endocardial borders of the LV walls during cavity opacification and, much more important, to define in detail the characteristics of the "in plus" image. When only a fraction of the initially administered SonoVue persisted at the myocardial level, the "in plus" image appeared to be simply due to an extension of the eosinophilic infiltrate to the myocardial walls of the posterior septum and lateral wall (apical 4-chamber view) as well as of the inferior and anterior walls (2-chamber view). The most typical finding shown by

SonoVue involved the papillary muscles and chordae tendinae of the mitral valve, both structures being extensively infiltrated and clearly visible almost throughout their course. The mechanism responsible for this imaging improvement is attributable to a delayed persistence of SonoVue into the endomyocardial structures, consequent to the slowing down of the cardiac microcirculation related to the endothelial alterations described in the hypereosinophilic syndrome[19]. Our findings could have probably been further improved had we used dedicated softwares for myocardial contrast agents, owing to the fact that "flashing"-derived SonoVue microbubble rupture is able to considerably ameliorate myocardial perfusion imaging.

The present case report highlights the usefulness of the myocardial contrast agent SonoVue in combination with tissue harmonic imaging, for the interpretation of non-contrast echocardiography and also for the differential diagnosis of cardiac masses. SonoVue allowed us to exclude the presence of cardiac thrombi. The findings of the present case report have clinical implications since an aggressive therapeutic management is desirable to prevent major cardiovascular complications in patients with the hypereosinophilic syndrome. The National Institute of Health has formulated a score to predict which patients with the hypereosinophilic syndrome will need intensive medical therapy[20]. This scoring system reflects the severity of aggressive disease in patients who present with cardiac or neurologic involvement or both. The use of SonoVue is desirable in such conditions, when a diagnosis made at non-contrast echocardiography would be uncertain.

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