Value of Two-dimensional Echocardiography in Endomyocardial Disease With and Without Eosinophilia

A Clinical and Pathologic Study

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SUMMARY Ten patients (six women and four men) with endomyocardial disease, four with and six without hypereosinophilia, were studied by two-dimensional echocardiography (2-D echo). Eight had biventricular congestive heart failure and two had atypical chest pain with ischemic electrocardiographic changes. The patients were 15–50 years old (mean 40 years) and duration of illness was 2–9 years (mean 4.4 years). Nine had cardiac catheterization and three pathologic examination.

Characteristic 2-D echo findings included apical obliteration of one or both ventricles by echogenic material suggestive of fibrosis or thrombosis; bright, specular echoes at the cavity surface of the apical obliteration suggesting patchy calcification; preserved left apical systolic inward motion, which differed significantly from the dyskinetic motion of thrombotic apical obliteration of ischemic or Chagasic origin (p < 0.001); involvement of the papillary muscles and posterior atrioventricular valve; preserved ventricular contractile function in most patients; and the combination of normal-to-small ventricles with large atria. None of 14 subjects with secondary hypereosinophilia followed for 15.4 months developed similar 2-D echo findings.

We conclude that both forms of endomyocardial disease had a 2-D echo pattern useful for noninvasive recognition and differentiation from patients who have valvular heart disease, constrictive pericarditis and cardiomyopathies of other origins.

ENDOMYOCARDIAL DISEASE (EMD) is a restrictive cardiomyopathy characterized pathologically by a striking endocardial fibrotic thickening that usually affects the apex of one or both ventricles. Described in Uganda by Davies as endomyocardial fibrosis, other cases have been reported from tropical and nontropical countries. Its recognition has been mainly established in endemic areas by its clinical picture, by the characteristic angiographic obliteration of the ventricular apex or at autopsy. Löffler described a similar pathologic picture in patients with eosinophilia, endocarditis parietal fibroplastica. Pathologic series suggest that both forms represent the spectrum of a single entity, EMD with or without eosinophilia. Because two-dimensional echocardiography allows the noninvasive assessment of cardiac function and anatomy (including the ventricular apex), we evaluated its usefulness in the recognition of this disorder.

Patients

This study was stimulated by an echocardiogram performed in 1977 on a patient with clinically diag-
spleenomegaly. Three patients with severe right heart failure and ascites had a peculiar facies that included puffy eyes, skin pallor and slightly cyanotic lips. This clinical picture resembled pericardial constriction.

Cardiac signs included elevated venous pressure in eight, outward systolic venous pulsations and/or prominent jugular a-wave in three, third heart sound in seven, mitral and/or tricuspid systolic murmurs in five, and diastolic murmurs in two. In the four patients with hypereosinophilic syndrome, constitutional symptoms were also present: fever, excessive sweating, pruritic skin rash and asthma in three, and mononeuritis multiplex, transient cerebral ischemic episodes, muscle pain and abdominal cramps in two each. One had repeated pulmonary infarctions.

In two patients without clinical heart failure, the major complaint was atypical chest pain, with electrocardiographic changes suggestive of ischemia. Because of these symptoms, both underwent coronary arteriography.

Duration of illness ranged from 2 to 9 years (mean 4.4 years). Six patients had increased eosinophil counts on two or more determinations (normal eosinophil values in our laboratory are < 0.55, hypereosinophilia > 1.5 x 10⁶/l, respectively). Searches for helminthic diseases were negative in all. Nine patients had cardiac catheterization. Three patients died in heart failure; two of them had hypereosinophilic syndrome and one died in the postoperative period after double valve replacement. Of the seven survivors, two with hypereosinophilic syndrome are improved and controlled with prednisone or hydroxyurea. Of the three patients with heart failure, two have worsened and one is stable. The two patients with atypical angina and normal coronary angiograms are symptomatically improved with oral isosorbide. The diagnosis of EMD was confirmed pathologically in three (one by endocardial biopsy and two by necropsy) and angiographically in seven.

We did not include in our series three additional patients with the clinical diagnosis of EMD; two refused to undergo angiography and in one patient, histologic examination of the heart showed nonspecific chronic myocarditis.

Control Groups

Three additional groups of subjects were also studied prospectively in order to compare their two-dimensional echocardiographic findings with those of our patients.

Normal Subjects

The normal group consisted of eight subjects (five men and three women), ages 18–51 years (mean 32 years). All were referred for evaluation of systolic murmurs judged innocent or for extrasystoles. None had any other clinical abnormality.

Angiographic Left Ventricular Apical Thrombi

Twelve patients (nine men and three women) had ventriculographically detected apical filling defects in the setting of apical dyskinesia. They were 34–76 years old (mean 47 years). Four had coronary heart disease with electrocardiographic evidence of anterior or anteroseptal myocardial infarction. The other eight had normal coronary angiograms. Four of those with normal coronary arteries had chronic Chagas' heart disease, three had dilated (congestive) cardiomyopathy and one had heart disease of unknown origin. None of these 12 patients had eosinophilia. Five had sustained acute ischemic cerebral events suspected of resulting from arterial emboli. One had necropsy confirmation of the combination of apical thrombus and central nervous system embolism.

Patients with Secondary Hypereosinophilia

Fourteen patients (eight males and six females) were recruited from the hematology service of the hospital.
of the University of Caracas, where they had been referred for evaluation of hypereosinophilia. They were 2–62 years old (mean 24 years). Mean and highest eosinophil counts ranged from 1.5 to 19.2 × 10⁹/l (mean 6.4 × 10⁹/l) and 2.8 to 38.5 × 10⁹/l (mean 11.7 × 10⁹/l), respectively. Before echocardiographic evaluation, they were followed for 2–48 months (mean 15.4 months). The diagnosis in 11 patients was helminthic infestation with single organisms in six and multiple organisms in five. Strongyloides stercoralis were identified in seven, Trichuris trichiura and Ascaris lumbricoides in three and Necator americanus, Ankylostoma duodenalis, Taenia solium and Toxocara canis in one. Of the other three patients, one had Paracoccidioides brasiliensis, one Churg-Strauss syndrome and one diffuse lymphocytic lymphoma, poorly differentiated.

**Methods**

M-mode and two-dimensional echocardiography was performed in all patients. In the initial phase of our study we used a mechanical, rotating-element sector scanner (Smith Kline Ekosector 1) and, later, a 32-element phased-array (Diasonic 3400R) system. Tracings were recorded for later playback and analysis using a variety of videotape recorders. Multiple views from several windows were obtained in the standard manner. Particular attention was paid to obtaining images from the apical impulse location. In all cases, care was taken to examine patients in extreme left recumbency. Additionally, biplanar images of the inferior vena cava from the subcostal window during quiet and exaggerated respiration were sought for the diagnosis of elevated right ventricular diastolic pressure. Semi-quantitative assessment of cardiac apical motion was performed by recording an M-mode tracing generated from an M-mode cursor passed through or near the apex of each ventricle. Gains were carefully adjusted during M-mode recording to enable assessment of the apical motion. This motion was expressed as a negative (outward) or a positive (inward) number. Because we could not always obtain a precise orthogonal placement of the M-mode cursor relative to the apex, myocardial motion was judged by the dominant movement occurring during systole. In four patients, we used contrast methods to better visualize the right ventricular apex, and thereby detect obliteration. Simultaneously, M-mode and two-dimensional images were recorded during the contrast effect. The contrast effect not only enhanced the two-dimensional image of the right ventricle, but also, on M-mode it helped to highlight wall motion and tricuspid insufficiency.

If the clinical status of the patient permitted, M-mode tracings were obtained during suspended respiration. In measuring motion of the apex, we appreciated the negative influence of tangential beam orientation on measurements, but we attempted to make this measurement as a semiquantitative means of expressing and analyzing our observations. To describe quantitatively the anatomic changes in our patients, we measured echocardiographically the volumes of the cardiac chambers from the apical view. Six patients were suitable for analysis. Stop-frame video images were digitized using a dedicated, microprocessor-controlled computer system (Diasonic 3400R). This system allows the operator to trace directly onto the cathode ray tube the endocardial chamber outline and long axis from which the computer calculated the volumes. The area-length formula of Dodge was the algorithm used in this study. We measured the left ventricular end-diastolic and the left and right atrial volumes at end-ventricular systole. Cardiac chamber volumes obtained with the method described above in a normal adult population were compared with those of our patients. The mean and 90% upper confidence bounds of the ninety-fifth percentile volumes were: in 52 subjects ages 20–66 years, left ventricular volumes in 29 males were 112 ml and 167 ml and in 23 females 89 ml and 129 ml; in 54 subjects ages 20–66 years, volumes for the left atria in 29 males were 41 ml and 64 ml and in 25 females 34 ml and 60 ml; for the right atria in males 41 ml and 68 ml and for females 27 ml and 41 ml, respectively.

The left ventricular/atrial volume ratios were calculated for the normal population and ranged from 2.15 to 2.73. Our normal M-mode values were also used for comparison.

Left and right ventricular cineangiograms were obtained in the standard right anterior oblique view after injection of Renografin-76. Coronary arteriography was performed using the Sones technique. For statistical analysis, an t test was used to compare mean differences between the normal subjects and other patient groups. Investigation of eosinophil abnormalities in blood smears was made retrospectively and prospectively. In our laboratory, normal eosinophils have <5% vacuoles and degranulation is absent.

**Results**

The two-dimensional echocardiographic appearance was similar in both forms of EMD, with and without eosinophilia.

**Apical Obliteration**

Apical obliteration was the most common finding and was observed in the left side in all 10 patients and the right side in eight. The apical obliteration appeared as distinct echogenic material superficially resembling apical thrombus, which in most subjects with left-sided lesions presented characteristically systolic inward motion. Figure 1 shows M-mode-measured left apical motion among the normal subjects and patients with EMD and apical thrombus. Both normal and EMD groups had left apical systolic inward motion, but this motion was significantly greater in the EMD patients (fig. 2). Mean values were 2.0 ± 1.5 (± sd) and 6.3 ± 5.5 mm, respectively (p < 0.05). In contrast, most patients with apical thrombi characteristically displayed an outward, or diskine tic, apical motion, with a mean of −1.8 ± 1.7 mm This value was opposite to and different from that seen by normal and EMD subjects (p < 0.001 for both).
echocardiography in five patients allowed delineation of the irregular surface of the right apical obliteratorative process and its extension (fig. 4).

Valves
The semilunar and anterior atrioventricular valve leaflets were unaffected in all patients. The posterior mitral valve adhered to a densely echogenic posterobasal ventricular wall in three subjects. In one, the appearance was similar to posterior submitral annular calcification. Three subjects with mitral regurgitation had shallow hammock systolic buckling. One subject showed erratic motion of the tricuspid valve, possibly because of turbulence. In a subject with dense fibrosis of the right ventricular inflow tract, the posterior tricuspid valve was thickened.

Interventricular Septum
While the apical portion appeared embedded in the obliteratorative process, the basal and midportion, with one exception, were spared. Systolic thickening and amplitude of motion were normal or increased in seven and paradoxical in three (one with right ventricular volume load, one with pericardial effusion and one with associated coronary artery disease). Two patients had abrupt, early diastolic anterior motion simultaneous with a prominent third heart sound.

Ventricles and Atria (table 2)
The four-chamber apical view provided the characteristic pattern of small ventricles with large atria due to the combination of apical cutoff and atrioventricular regurgitation (figs. 2 and 3).

Two-dimensional echocardiographic left ventricular volumes were normal or decreased in five of six patients, ranging from 35 to 154 ml (mean 86 ml). Left atrial volumes were increased in four patients, ranging from 38 to 89 ml (mean 67 ml), and the right atrial volumes were also increased in five patients, ranging from 31 to 188 ml (mean 96 ml). The left ventricular/atrial volume ratio was decreased in five patients, with
values ranging from 0.49 to 3.14 (mean 1.48). The exceptions were case 3, who had dilated left ventricle, and cases 3 and 7, with normal-sized left atria. M-mode echocardiographic left ventricular diastolic dimensions ranged from 42 to 66 mm (mean 51 mm) and left atrial end-systolic dimensions from 32 to 58 mm (mean 42 mm).

Left ventricular function was normal or increased by M-mode echocardiographic percent fractional shortening in six of seven subjects, ranging from 24% to 45% (mean 38%) and by angiographic left ventricular ejection fraction in seven of nine patients, ranging from 28% to 81% (mean 62%).

Right ventricular dysfunction was suspected by poor inspiratory size decrease of a grossly dilated inferior vena cava in six of seven subjects in whom this sign was sought. In two patients with isolated left ventricular involvement, the inferior vena cava was normal.

Other Findings
Two patients had pericardial effusion during their clinical course. Case 4 required pericardiocentesis, but at surgery the pericardium was normal. In case 3 the effusion disappeared simultaneously with medical treatment.

Cardiac Catheterization (table 3)
Typical\(^6,7\) angiographic apical obliteration was found on the left in nine patients and on the right side in seven. In six patients, on the left side the ventricular shape looked globular with normal or hyperdynamic contracting walls. In five patients, end-diastolic ventricular pressures were increased on both sides. A "dip-and-plateau" diastolic pressure tracing was observed in almost all subjects with increased pressures. The right ventricular apical shape was grossly distorted by the obliteration, which was, itself, irregular. Often,
the outflow tracts were dilated. Five patients had major mitral and tricuspid regurgitation. The coronary arteries were normal in all except patient 10.

### Secondary Hypereosinophilia

During a mean follow-up of 14.5 months, none of the 14 patients with secondary hypereosinophilia developed cardiac lesions similar to those presented by patients with EMD. One patient had a previous dilated cardiomyopathy historically unrelated to his eosinophilic process. All subjects with helminthic or mycotic diseases were successfully treated.

### Pathology

Patients 1 and 2 underwent examination at necropsy. They had biventricular apical obliteration by endocardial fibrosis approximately 3–5 mm thick that extended to the corresponding inflow tract, reaching the mitral papillary muscles and posterior mitral valve. On the right side, in case 1 the fibrosis stopped abruptly 1 cm below the posterior tricuspid valve, encasing the posterior tricuspid papillary muscle; in case 2 the fibrosis encompassed the tricuspid posterior valve leaflet which was thickened and fibrotic. In both, the atria were dilated. Histologic examination showed typical changes, consisting of a prominent layer of hyaline fibrous tissue in the thickened endocardium, inflammatory cells and dilated vessels between the hyaline tissue and the myocardium. In case 4, surgical biopsy disclosed endocardial fibrotic layers reaching the myocardium through fine septa. None of the patients had myocardial eosinophilic infiltration.

### Eosinophil Abnormalities

Blood smears were examined in six of 10 patients with EMD and in nine of 14 with secondary hypereosinophilia. Patients 1 and 2 had eosinophil degranulation and patients 1, 2, and 9 had increased vacuoles. One patient with secondary hypereosinophilia had degranulation and five had increased vacuoles.

### Discussion

We have found that two-dimensional echocardiography is useful in the noninvasive recognition of EMD. A combination of findings consisting of apical obliteration, preserved contractile ventricular function, thickening of the mitral and/or tricuspid posterior valves, and grossly dilated atria appears to be unique to this condition (fig. 5). The echocardiographic differentiation of apical thrombus from apical obliteration poses difficulties, because their appearance may be similar. In myocardial infarction or cardiomyopathy, the thrombi are superimposed on a hypo- or dyskinetic ventricular wall. In EMD, however, the myocardial contraction underlying the obliterative process continues and the apex retains its inward motion.

Although apical obliteration is found in most EMD patients, not all demonstrate this finding. Shaper and co-workers, in one of the largest series of endomyocardial fibrosis patient autopsies from Uganda, described five patterns of lesion distribution in the left or right ventricles: type 1 — affects the apex only; type 2 — extends from the apex to the atroventricular valve; type 3...
type 3 — valve lesions only; type 4 — lesions in the apex and valvular regions (not affecting intervening endocardium); and type 5 — patches in areas other than the apex or valves. In the present series, all of our patients corresponded to types 1 and 2. We initially included in our group a patient with a presumptive type 3 lesion of the posterior mitral valve because of the general appearance of small ventricles with large atria. We could not echocardiographically demonstrate apical obliteration. Necropsy disclosed a chronic myocarditis of unknown origin with severe lymphocytic infiltration especially of the left atria. The posterior mitral valve and posterobasal endocardium had nonspecific thickening and fibrosis. Therefore, in the absence of an apical lesion, EMD type 3 lesions, and possibly type 5 lesions, might be difficult to diagnose.

In our four patients with hypereosinophilic syndrome, two (cases 1 and 2) died as the result of the cardiovascular lesions after a clinical history of 6 years, and two (cases 3 and 8), who had early treatment either with prednisone or with hydroxyurea, showed encouraging results. However, although ventricular function improved during therapy, it did not prevent the progressive development of biventricular apical obliteration. Spry and colleagues emphasized that degranulated eosinophils in the blood smear are important evidence favoring potential cardiac damage even in the absence of frank eosinophilia. We found degranulated eosinophils in two of our patients with EMD. However, most of our subjects were studied at their fibrotic stage, months or years after the clinical beginning of their disease, when eosinophil abnormalities, if present initially, were absent. In the group with secondary hypereosinophilia, we have not observed lesions similar to our group with EMD despite persistent eosinophilia (in some for more than 6 months) or eosinophil abnormalities. The observation period in these patients was just over 15 months, as opposed to 4 years in EMD patients. Thus, a longer follow-up might be necessary to rule out the development of echocardiographic lesions in secondary eosinophilia.

In patients 6 and 9, who clinically presented with atypical chest pain and ischemic electrocardiographic changes, angiography disclosed normal coronary arteries and typical (type 1) left ventricular isolated apical obliteration. These two patients are similar to those described from England, clinically simulating ischemic coronary heart disease. This presentation contrasts with other series from Africa, in which most patients presented with congestive heart failure but none with chest pain. M-mode echocardiograms were also frequently abnormal in patients with EMD. Findings included distinct, intense echoes from the affected endocardium, thickening of the posterior mitral valve, septal wall motion abnormalities, abrupt early diastolic left ventricular posterior wall motion, normal minor-axis cavity size, and usually normal to hyperdynamic ventricular function. Nevertheless, M-mode echocardiography, lacking the spatial representation of two-dimensional echocardiography, failed to demonstrate apical obliteration. More recently, the use of color-coded, amplitude-processed, two-dimensional echocardiography has allowed others to identify abnormally high intensity echoes from areas of presumed fibrosis at the ventricular apex and inflow tracts in patients with eosinophilic EMD at an early stage.

Clinically and hemodynamically, severe EMD and constrictive pericarditis have similarities. In constrictive pericarditis, two-dimensional echocardiography might present the combination of small-appearing ventricles, normal atria and, in most, increased pericardial echoes. In our EMD patients, the pericardium appeared normal in all and atrial enlargement was prominent in most. The differentiation of valvular EMD from valvular heart disease or rheumatic heart disease (cases 2 and 5) is made by the combination of findings.

Two of our patients had diminished left ventricular function, in one patient (case 10) because of coronary heart disease and in one (case 3) because of acute myocarditis in the setting of idiopathic hypereosinophilic syndrome. Therefore, diffuse hypokinesis in the setting of suspected EMD should arouse suspicion of an associated disorder. Furthermore, in patients with an atypical echocardiographic pattern and/or eosinophilia, endocardial biopsy should help establish a diagnosis of eosinophilic EMD.

We conclude that two-dimensional echocardiography is useful for diagnosing both forms of EMD and should prove of value in prompt recognition of this disorder and, perhaps, in its subsequent management.

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