Two-dimensional Echocardiographic Assessment of the Idiopathic Hypereosinophilic Syndrome

Anatomic Basis of Mitral Regurgitation and Peripheral Embolization

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SUMMARY Important cardiac manifestations in the idiopathic hypereosinophilic syndrome include mitral regurgitation and peripheral embolization. To determine the anatomic basis of these abnormalities, real-time, wide-angle, two-dimensional echocardiography (2-D echo) was performed in 21 patients with the hypereosinophilic syndrome. Nine patients (43%) had clinical evidence of mitral regurgitation, and each had localized thickening of the posterobasal left ventricular wall behind the posterior mitral leaflet and absent (seven patients) or diminished (two patients) motion of the posterior leaflet. Anatomic observations at operation or necropsy in four patients with mitral regurgitation demonstrated that the echocardiographic abnormalities resulted from posterior mitral leaflet thickening and adherence of the leaflet to the underlying mural endocardium of the posterobasal wall. On 2-D echo, each of the six patients with peripheral emboli had either apical left ventricular echo-dense targets consistent with thrombus or thickening of the posterobasal wall of the left ventricle, and these findings were validated at autopsy or operation in three patients.

Hence, in patients with the hypereosinophilic syndrome, 2-D echo is useful in identifying the probable etiology of two important cardiac manifestations. Thickening of the posterobasal wall is usually associated with impairment of posterior mitral leaflet function, resulting in mitral regurgitation. Because the hypereosinophilic syndrome is associated with peripheral embolization, thrombus formation and subsequent endocardial scarring, the noninvasive identification of intracavitary ventricular thrombi may be important.

CARDIAC INVOLVEMENT is a major cause of death in the idiopathic hypereosinophilic syndrome, a systemic illness characterized by a persistently elevated blood eosinophil count without an identifiable etiology for the eosinophilia.1,2 Although almost any organ may be affected, cardiovascular abnormalities have been identified in most patients.3 Roberts et al.4 suggested that intracavitary thrombi and extensive endocardial fibrosis are causally related to the occurrence of restrictive cardiomyopathy, atrioventricular valve abnormalities (particularly mitral regurgitation) and peripheral embolism. To determine the morphologic cause of the mitral regurgitation and peripheral embolization, wide-angle two-dimensional echocardiography (2-D echo) was performed in 21 patients with the hypereosinophilic syndrome, and the findings were compared with other clinical features.

Methods

Patients

Twenty-one consecutive patients with the idiopathic hypereosinophilic syndrome who had been identified prospectively at the National Institutes of Health constitute the study group (table 1). All patients had been admitted to the clinical center and extensively evaluated to exclude other causes of peripheral blood eosinophilia. The details of this diagnostic evaluation have been described.5

The criteria for diagnosis of the idiopathic hypereosinophilic syndrome included a persistent, total eosinophil count of more than 1500 cells/mm3; an extensive evaluation that excluded other known causes of hypereosinophilia, such as parasitic infection, allergy or neoplasm; and clinical or biopsy evidence of organ system involvement. All patients except 1, 3, 6, 7, 9 and 16 (table 1) were being treated with prednisone or hydroxyurea or both at the time of the echocardiographic recording.

Clinical Evaluation

The diagnosis of mitral regurgitation was based on the identification of an apical holosystolic murmur that responded appropriately to bedside physiologic maneuvers. The murmur decreased in intensity with the Valsalva maneuver and with the administration of amyl nitrate, and increased in intensity with squatting. In patients 5, 8 and 10, left ventriculography confirmed the presence of marked mitral regurgitation; each patient subsequently underwent mitral valve replacement. A history of transient ischemic attacks (three patients), or cerebrovascular accident (three patients) was considered evidence of previous peripheral embolism.

Echocardiographic Evaluation

Two-dimensional echocardiograms were obtained with a commercially available, real-time, phased-ar-
ray, 80° ultrasonic sector scanner (V3000 or 3400) using a hand-held 2.25-MHz transducer. Echocardiograms were recorded on either one-half-inch cassette videotape, 1-inch reel-to-reel videotape, or a rhodium-plated chromium disc for subsequent review in real-time, slow-motion or stop-action mode. Single-frame photographs were made from the television monitor using a 35-mm camera.

Two-dimensional echocardiographic examination included the imaging of a number of cross-sectional planes through the heart.6-8 Serial short-axis views of the left ventricle were obtained by orienting the sector plane perpendicular to the long axis of the left ventricle from a standard transducer placement on the chest. The short-axis sweep was performed by maintaining the transducer in a fixed location on the chest wall and slowly angling the image plane from aorta (cephalad) to apex (caudad). Care was taken to assure proper transducer angulation so that the left ventricle appeared circular rather than oval or elliptical.

The long-axis view was obtained by orienting the sector plan parallel to the longitudinal axis of the left ventricle, taking care to avoid improper angulation of the scan plane tangentially through the ventricle. The apical four-chamber view was obtained with the transducer placed at the cardiac apex and the tomographic plane directed perpendicular to the ventricular and atrial septa and through the plane of the mitral and tricuspid valve orifices to permit simultaneous display of both atria and ventricles, atrioventricular valves and cardiac septa.

Two-dimensional echocardiograms were reviewed independently by two of the authors, one of whom was unaware of the clinical findings. Increased posterobasal wall thickness was identified in the parasternal long-axis view as an abrupt displacement of the endocardial contour at the level of the posterior mitral leaflet, so that the posterobasal region was substantially thicker than was the ventricular free wall distal to the mitral leaflets. This "thickening" of the posterobasal wall was considered to represent either recent thrombus formation, organizing thrombus, or scarring superimposed on the posterobasal left ventricular wall (which itself was of normal or slightly increased thickness).4,9,10

Echocardiograms were interpreted as showing absent or markedly limited posterior mitral leaflet motion if no leaflet motion, or only a barely perceptible sug-

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**TABLE 1. Clinical Features in 21 Patients with Hypereosinophilic Syndrome**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Highest eosinophil count (mm³)</th>
<th>Duration of illness (years)</th>
<th>First organ system involved†</th>
<th>MR</th>
<th>PE</th>
<th>Apical LV cavity density</th>
<th>Abnormal PML motion</th>
<th>Thickened P-B LV wall</th>
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*Evaluation 11 months previously showed no 2-D echocardiographic abnormalities or clinical evidence of either mitral regurgitation or peripheral emboli.

†Evaluation 3 months previously showed no 2-D echocardiographic abnormalities or clinical evidence of peripheral embolization; mitral regurgitation, however, was present.

‡Exclusive of bone marrow.

Abbreviations: GI = gastrointestinal; LV = left ventricular; MR = mitral regurgitation; P-B = posterobasal; PE = peripheral emboli; PML = posterior mitral leaflet; 2-D echo = two-dimensional echocardiography.
gestion of motion, was evident in all three echocardiographic image planes. Left ventricular thrombus was considered present if an echo density with distinct margins was present within the ventricular cavity in continuity with the endocardium, but unassociated with the papillary muscles.11-13

Pathologic Studies

Material for pathologic examinations was available in four patients. In three, the mitral valve had been excised at operation14 2–4 weeks after the echocardiographic study; one patient was studied at necropsy 6 months after the echocardiographic studies.

Results

Mitral Regurgitation

Mitral regurgitation was identified in nine patients (table 1). In each, the 2-D echo showed increased thickness (range 15–26 mm) of the portion of posterobasal left ventricular wall behind the posterior mitral leaflet (fig. 1). The M-mode echocardiogram (fig. 2), recorded simultaneously and under direct visualization with the 2-D echo, confirmed that the posterobasal wall at the level of the mitral valve was markedly thickened compared with the left ventricular free wall distal to the mitral valve. Each patient with mitral regurgitation and posterobasal wall thickening had ab-
FIGURE 3. Two-dimensional echocardiogram during diastole in apical four-chamber view from patient 5. Note the apically displaced structure (arrow), which showed motion characteristic of mitral valve on real-time display. The proximal (basilar) portion of this leaflet is not visible because of incorporation within echo-dense material (arrowhead), representing organized thrombus, extending from left ventricular inflow tract. AML = anterior mitral leaflet; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; VS = ventricular septum.

FIGURE 4. Gross anatomic findings in patient 4, who had severe mitral regurgitation. (A) View of left ventricular inflow tract showing the anterior (A) and posterior (within box) leaflets and their chordal attachments to the papillary muscles. The anterior leaflet is normal, but the posterior leaflet is scarred and adheres to the posterior left ventricular wall. (B) Closer view of the fixed posterior leaflet shown within the box in panel A. Broken line indicates the plane of section producing the view of the left ventricular inflow tract seen in panel C. (C) Posterobasal left ventricular free wall showing substantial endocardial scarring which has obliterated the posterior mitral leaflet except for the area indicated by the arrow. (D) Photomicrograph of histologic section taken from panel C, stained with hematoxylin-eosin. (E) Inflow tract of right ventricle (RV) shows endocardial scarring (within broken line). LA = left atrium; LV = left ventricle; RA = right atrium; TV = tricuspid valve.
sent (seven patients) or diminished (two patients) motion of the posterior mitral leaflet. In the two patients with diminished motion, no posterior leaflet motion could be visualized in the parasternal long- or short-axis views; however, the apical four-chamber view demonstrated that only the most distal "apical" portion of the posterior mitral leaflet was mobile (fig. 3). Leaflet motion was not evident in the proximal portion of the posterior leaflet, presumably because it adhered to the posterobasal wall. This alteration of mitral valve anatomy also appeared to prevent normal systolic coaptation between the posterior and anterior mitral leaflets. Patients 15 and 18, without evidence of mitral regurgitation, had increased posterobasal wall thickness, but both had normal mitral leaflet motion.

Anatomic confirmation of the mitral valve abnormality identified by 2-D echo (figs. 1 and 3) was available in four patients. In each, the posterior mitral leaflet was thickened and adherent to the underlying endocardium of the posterobasal wall (fig. 4), by virtue of its incorporation within accumulations of calcified and fibrotic material attached to the mural endocardial surface. In addition, in patient 5, thrombus also was present on the tricuspid valve leaflets and the anterior mitral leaflet, which were partially destroyed.

Peripheral Embolization

Each of the six patients with clinical events suggestive of peripheral emboli had evidence by 2-D echo of thrombus formation in either the left ventricular apex (two patients) or left ventricular inflow tract (two patients) or both (two patients) (figs. 5 and 6). Of the 15 other patients who did not have clinical events compatible with peripheral embolization, 10 had evidence of intraventricular thrombus, three in the left ventricular apex and seven in the inflow tract.

Supporting evidence or anatomic confirmation for the 2-D echo finding of apical left ventricular thrombus was available in five patients; an apical thrombus was observed at operation in patients 5, 8 and 10 and at
susceptible reported organized, fibrotic ease, on posterior mitral tissue. Davies,9 noted ventricular gurgitation the leaflet and the submitral angle free wall operation at LV = left ventricle.

Our findings regarding the mechanism of mitral regurgitation in hypereosinophilic syndrome support the observations of Davies9 and Brockington and Olsen.10 Davies,9 in a necropsy study of patients with this disease, reported thickening of the posterior mitral leaflet and noted that the leaflet in some patients adhered to organized, fibrotic thrombus on the surface of the posterior left ventricular wall. Brockington and Olsen10 reported three patients with this disease in whom the posterior mitral leaflet was incorporated within the fibrotic tissue.

We hypothesize that turbulence of blood flow in the left ventricular inflow tract and apex make these sites on the endocardial surface of the left ventricular wall particularly susceptible to eosinophilic injury and subsequent thrombus formation. Thereafter, clot organization, scarring and new thrombus formation occurs. Eventually, the posterior mitral leaflet motion is impaired or abolished as the leaflet becomes adherent to, and ultimately incorporated in, the scar and thrombus. The extension of thrombus to adjacent endocardial surfaces followed by thrombus organization and subsequent scarring may result in a restrictive-type ventricle.

Two-dimensional echocardiography was of value in identifying left ventricular thrombi in our patients and also was a sensitive method of identifying patients with hypereosinophilic syndrome who were at risk for peripheral embolization. Each of the six patients with peripheral emboli had evidence of intracavitary thrombi by 2-D echo, including four with thrombi in the apex of the left ventricle. Ten other patients without peripheral embolization also had echocardiographic evidence of thrombus formation, however, either in the left ventricular inflow tract or apex. Nevertheless, because of the relatively high incidence of peripheral emboli in patients with the hypereosinophilic syndrome, patients with evidence of intraventricular thrombi should be considered at risk for peripheral emboli, and hence are candidates for chronic anticoagulation therapy. Patients with thrombus in the left ventricular inflow tract alone may also be at risk for peripheral embolization, of course, since such posterobasal wall “thickening” may represent fresh thrombus. In contrast, patients with the hypereosinophilic syndrome who do not have either posterobasal wall thickening or apical thrombi by 2-D echo do not appear to be at substantial risk of embolization. Anticoagulation therapy may modify the development of the restrictive ventricle in the hypereosinophilic syndrome, which appears to be the consequence of organization of intraventricular thrombi and subsequent widespread endocardial scarring.

The rapidity with which this process may evolve in patients with hypereosinophilic syndrome is illustrated by patient 13, who had a cerebral embolus and severe mitral regurgitation at a time when he had 2-D echo evidence of left ventricular apical and inflow tract thrombus, with fixation of the posterior mitral leaflet on 2-D echo (fig. 6). Just 3 months previously, echocardiographic studies had failed to demonstrate thrombus in the left ventricle and the posterior mitral leaflet was normal.

Thus, marked limitation of posterior mitral leaflet motion by adherence to and eventual incorporation within thrombus and scar on the posterobasal endocardial surface of the left ventricle inflow tract is the mechanism by which mitral regurgitation occurs in patients with the hypereosinophilic syndrome. Posterobasal wall thickening and apical left ventricular echo densities suggest the presence of intraventricular thrombi, which are the source of systemic emboli and the cause of the subsequent development of a restrictive ventricle. These findings (fig. 8) may be reliably determined...
detected by 2-D echo, which is, therefore, a useful adjunct in the cardiac evaluation of patients with the hypereosinophilic syndrome.

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Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome. Anatomic basis of mitral regurgitation and peripheral embolization.
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