Supravalvular Aortic Stenosis and Coronary Ostial Stenosis in Familial Hypercholesterolemia: Two-dimensional Echocardiographic Assessment

SHINTARO BEPPU, M.D., YASUHARU MINURA, M.D., HIROSHI SAKAKIBARA, M.D., SEIKI NAGATA, M.D., YUNG-DAE PARK, M.D., SEIKI NAMBU, M.D., AND AKIRA YAMAMOTO, M.D.

SUMMARY The lesions of the aortic root, which are supravalvular aortic stenosis and coronary ostial stenosis, in familial hypercholesterolemia were studied using two-dimensional echocardiography. The subjects were 25 heterozygotes, six homozygotes and 30 control subjects.

The internal diameters of the aortic ring, the sinus of Valsalva and the supravalvular aortic ring were measured. Measurement variation due to body size was avoided by normalizing the latter two values by the diameter of the aortic ring. Four heterozygotes and all homozygotes were judged to have stenosis of the supravalvular aortic ring; none of heterozygotes and four homozygotes had stenosis of the sinus of Valsalva. In three of the four patients with stenosis of both the supravalvular aortic ring and the sinus of Valsalva, a pressure gradient was demonstrated. The degree of supravalvular aortic stenosis correlated with the serum cholesterol level but not with patient age. All homozygotes, even very young ones, had a severe aortic root lesion. In the short-axis view of the aortic root, a lump (raised mass) on the aortic wall indicating atheromatous plaquing was demonstrated in five heterozygotes and all homozygotes. Coronary ostial stenosis was shown in three of the four patients whose plaquing echoes were adjacent to the coronary orifice.

We conclude that two-dimensional echocardiography is useful in diagnosing lesions of the aortic root in patients with hypercholesterolemia.

IT HAS BEEN generally recognized that a high level of serum cholesterol causes atheromatous change of the aorta to progress. In familial hypercholesterolemia especially, the atheromatous plaquing on the aortic root is significant and results in supravalvular aortic stenosis or ostial stenosis of the coronary artery in some patients. These complications are fatal and an accurate diagnosis is vital. These aortic root lesions have been diagnosed by angiography or observed at autopsy. The aim of the present study was to examine the usefulness of two-dimensional echocardiography in diagnosing these lesions and to extract the characteristic features of this disease in comparison with other clinical findings.

Methods

Patients

Sixty-one patients were examined and divided into three groups (table 1).

Control Group

The control group consisted of 30 patients whose serum cholesterol levels were normal and whose two-dimensional echocardiograms of the aortic root were recorded clearly. There were 12 males and 18 females, ages 3–78 years (average 47.3 years). Serum cholesterol ranged from 114 to 258 mg/dl (average 187 mg/dl). Ten patients had cardiac arrhythmia, seven mild systemic hypertension and six neurocirculatory asthenia; seven of the control subjects were healthy. None had xanthoma or aortic ejection murmur.

Heterozygote Group

The heterozygotes consisted of 25 patients heterozygous for familial hypercholesterolemia. There were 12 males and 13 females, ages 13–71 years (average 43.6 years). The diagnosis was based on the high serum cholesterol level with normal triglyceride level, familial history, and thickening of the Achilles tendon or skin xanthoma. Serum cholesterol ranged from 294 to 468 mg/dl (average 345 mg/dl). The thickness of the Achilles tendon was greater than 9 mm on the ankle x-ray in each patient. Skin xanthoma, other than xanthelasma, was noted in nine patients. An aortic ejection murmur was audible in six patients. None of the six patients who underwent cardiac catheterization and coronary angiography had a pressure gradient at the supravalvular level or coronary ostial stenosis.

Homozygote Group

The homozygotes consisted of six patients homozygous for familial hypercholesterolemia. There were three males and three females, ages 3–38 years (average 20.0 years). The defect of the low-density lipoprotein receptor was revealed by a skin biopsy in all patients. Serum cholesterol ranged from 593 to 820 mg/dl (average 702 mg/dl average). Xanthomas on the skin or the tendon were noted in all patients. An aortic ejection murmur was audible in all patients, and a pressure gradient at the supravalvular level was noted in four of the five patients who underwent cardiac catheterization. Selective coronary angiography showed ostial stenosis of the coronary artery in three of these five patients.

The clinical data of the subjects are summarized in table 1.

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From the National Cardiovascular Center, Research Institute and Hospital, Osaka, Japan.
Supported in part by a research grant for cardiovascular disease (56C-9) from the Ministry of Health and Welfare of Japan.
Address for correspondence: Shintaro Beppu, M.D., National Cardiovascular Center, Research Institute, 5-chome, Fujishirodai, Suita, Osaka 565 Japan.
Received May 18, 1982; revision accepted November 29, 1982.
Circulation 67, No. 4, 1983.
Echocardiography

The equipment used was a commercially available electronic phased-array system (Toshiba SSH-11A). The patient was examined in the left recumbent position. The long-axis and short-axis views of the aortic root were recorded at end-diastole by the upper parasternal approach. In the long-axis view, the internal diameters of the aortic ring, the sinus of Valsalva and the supravalvular ring were measured (fig. 1). The supravalvular ring was defined as the narrowest site of the distal end of the sinus of Valsalva. Because the subjects were 3–78 years old, the raw value of the internal diameter was thought to be influenced by body size. Therefore, the internal diameters of the sinus of Valsalva and the supravalvular ring were normalized by the internal diameter of the aortic ring.

Table 1. Summary of Clinical and Echocardiographic Data

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Heterozygotes

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Abbreviations: Chol = serum cholesterol; Xanth = xanthoma; SM = systolic aortic ejection murmur; R = internal diameter of aortic ring; V = internal diameter of sinus of Valsalva; S = internal diameter of supravalvular ring; Pr.G = pressure gradient; Lump = lump on the aortic wall.
The short-axis view of the aortic root was continuously recorded from the distal site of the aorta to the sinus of Valsalva by tilting the transducer slowly, and the presence and location of the lump on the aortic wall by atheromatous plaquing were determined.

The two-dimensional echocardiographic findings were compared with the patients' clinical data.

**Results**

In the control group, the average normalized value of the sinus of Valsalva was 1.29 ± 0.15 (± SD); for the supravalvular ring, the average value was 1.07 ± 0.12. For the sake of convenience, stenosis of the sinus of Valsalva and of the supravalvular ring was designated at values lower than 0.99 and 0.83, respectively. These values represent 2 standard deviations below the average (table 1). The short-axis view of the aortic root was almost circular without any lump on the wall.

Sufficiently clear two-dimensional echocardiograms were recorded in 21 of the 25 heterozygotes. The aortic root echo was obscure in two patients and the supravalvular ring echo was not detected in another two patients. The averages of the normalized values of the sinus of Valsalva and of the supravalvular ring were 1.26 and 0.95, respectively (table 1). The latter value was significantly different from the average in the control group (p < 0.01), although the former was not. The echocardiographically defined stenosis of the supravalvular ring was shown in four patients (cases 1, 5, 19 and 20). One of these, case 20, underwent angiography and was shown to have a narrowed supravalvular ring. None showed the echocardiographically defined stenosis of the sinus of Valsalva. In the short-axis view, a lump on the aortic wall indicating atheromatous plaque was detected in five of the 25 patients, although the lump was not very prominent.

Echocardiograms of the aortic root were recorded clearly in all six homozygotes. The averages of the normalized values of the sinus of Valsalva and of the supravalvular ring were 0.92 and 0.59, respectively (both p < 0.001 vs control and heterozygote groups). The echocardiographically defined stenosis of the supravalvular ring was shown in all patients and that of the sinus of Valsalva in four patients. The narrowing of the aortic root demonstrated by two-dimensional echocardiography was also shown by aortography in five patients. In case 28, for example, stenosis of the supravalvular ring and of the sinus of Valsalva and poststenotic dilatation could be demonstrated by either method (figs. 2 and 3).

In the short-axis view, atheromatous plaque was detected in all of the patients. In four of the patients, the lump was obvious and located near the orifice of the left coronary artery (fig. 4). In three of these four patients, selective coronary angiography revealed ostial stenosis of the coronary artery.

In the hypercholesterolemia groups, an aortic ejection murmur was audible in nine of the 10 patients with stenosis of the supravalvular ring. All four patients with a pressure gradient at the supravalvular level had stenosis of the supravalvular ring, and three of them also had stenosis of the sinus of Valsalva.

Among the three groups, the normalized values of the internal diameter of the sinus of Valsalva and of the supravalvular ring indicated a good linear correlation (r = 0.77, p < 0.001). The hypercholesterolemia patients are located to the left of the control patients in the diagram (fig. 5).
was thickened and the echo intensity was pronounced, suggesting calcification. The leaflet did not bend in any phase of the cardiac cycle, suggesting loss of flexibility. The short-axis view of the anterior leaflet showed that the thickening and hardening of the leaflet was not uniform and that the shape of the leaflet was distorted (fig. 8). There was no finding to suggest commissural fusion. This patient died after aortocoronary bypass for resolving angina pectoris. Autopsy revealed that the mitral leaflet was hardened by atheroma deposition and was calcified in part.

**Discussion**

**Supravalvular Aortic Stenosis**

Type IIa hyperlipidemia is related to atherosclerosis. Usually, the atheromatous plaquing of the aorta is most severe in the abdominal aorta. However, in homozygous familial hypercholesterolemia, there is a reverse phenomenon of atherosclerosis: the plaquing of the aortic root is more significant than the change in the abdominal aorta and results in supravalvular aortic stenosis. It is also a significant problem that severe atheromatous plaquing occurs in youth. Frequent examinations are needed to diagnose supravalvular aortic stenosis and ostial stenosis of the coronary artery in the early stage to avert sudden death. Therefore, noninvasive examination is preferred for diagnosing the aortic root lesion; until now, however, there has been no study using echocardiography.

In the present study, the internal diameters of the aortic ring, sinus of Valsalva and supravalvular ring were measured from two-dimensional echocardiograms to diagnose supravalvular aortic stenosis. To eliminate variations due to body size, we normalized the internal diameters of the sinus of Valsalva and of the supravalvular ring by the internal diameter of the aortic ring. Congenital supravalvular aortic stenosis and aortic hypoplasia have been diagnosed when the internal diameter of the ascending aorta was smaller than 75% of the internal diameter of the aortic ring. In the present study, on a statistical basis, 99% and 83% were the values used to diagnose stenosis in the sinus of Valsalva and in the supravalvular ring, respectively. Every patient with a pressure gradient at the supraval-

![Aortogram of the same patient as in figure 2. The large arrow indicates the stenotic site of the supravalvular aortic root. The small arrow indicates the thickened aortic valve.](image)

**FIGURE 3.** Aortogram of the same patient as in figure 2. The large arrow indicates the stenotic site of the supravalvular aortic root. The small arrow indicates the thickened aortic valve.

The narrowing of the sinus of Valsalva or the supravalvular ring did not correlate with patient age (r = 0.41 and r = 0.40, respectively). Among homozygotes, severe narrowing of the aortic root was present even in the 3-year-old patient (fig. 6).

The normalized internal diameters of the sinus of Valsalva and of the supravalvular ring correlated negatively with serum cholesterol value (r = −0.57 and r = −0.77, respectively) (fig. 7).

The coexistence of xanthoma and the narrowed aortic root was supported statistically in the homozygote group (p < 0.005 by chi-square test), but not in the heterozygote group (p < 0.25).

Thickening of the aortic valve was shown only in two homozygotes (cases 28 and 29). In the other patients in the three groups, no aortic valve lesion was demonstrated.

Two-dimensional echocardiography demonstrated a mitral valve lesion in one patient (case 28). The leaflet...
internal diameter of the aortic ring in these sites. Even if these values are applied to the present study, the results are not altered fundamentally.

Although the normalized internal diameter of the sinus of Valsalva and that of the supravalvular ring showed a linear correlation, the average of the normalized diameter of the sinus of Valsalva among heterozygotes was not different from that in the control group. This finding suggests that the atheromatous plaquing proceeds from the supravalvular ring to the sinus of Valsalva, a concept supported by autopsy studies.\textsuperscript{2, 6}

**Ostial Stenosis of the Coronary Artery**

One may assume that the atheromatous plaquing of the wall of the aortic root results in ostial stenosis of the coronary artery, which is located at the upper part of the sinus of Valsalva. Most patients with familial hypercholesterolemia suffer from ischemic heart disease. Especially in homozygotes, sudden death befalls many of the patients, even the young. In some of these cases, autopsy reveals coronary ostial stenosis by atheroma despite the lack of significant stenosis of the branches of the coronary arteries.\textsuperscript{2, 6} Therefore, the ostial stenosis must be diagnosed accurately. Stenosis of the coronary artery is diagnosed by angiography. However, by selective coronary angiography, as the contrast medium is injected from the catheter tip at a point past the ostium, it is difficult to show the relationship between the ostium of the coronary artery and the atheromatous plaque of the aortic wall. In the present study, we attempted to demonstrate ostial stenosis due to atheromatous plaquing by observing the short-axis views of the aortic root while tilting the transducer carefully. The two-dimensional echocardiographic approach to the proximal portion of the coronary artery has been reported.\textsuperscript{11} If the lump on the aortic wall was demonstrated adjacent to the coronary orifice, ostial stenosis was considered a possibility. Positive findings to this effect were recorded in three patients who had the left coronary ostial stenosis by angiography.

Two-dimensional echocardiography visualizes whether the atheroma has extended to the orifice of the coronary artery and is considered clinically useful.
Other Cardiac Lesions

The aortic valve was shown by two-dimensional echocardiography to be hardened in two patients. However, they were homozygotes and their supravalvular aortic stenosis was severe. It is thought that the aortic valve lesion is not primary, but results from the atheromatous change of the aortic wall. Findings at surgery or autopsy have shown that the aortic stenosis is not caused by the aortic valve but by the atheroma of the aortic root.\(^4\)\(^-\)\(^9\)

In one homozygote, the mitral valve also exhibited the atheromatous deposition (case 28). A few cases have been reported in which the mitral valve was involved by atheroma deposition. Most of these cases were not diagnosed as having mitral valve lesion until autopsy.\(^2\)\(^-\)\(^3\) The mitral valve lesion in patient 28 was not diagnosed until the echocardiographic examination. Although the echocardiographic findings of the mitral valve were similar to those of rheumatic mitral valve disease, the characteristic lack of mitral commissural fusion despite severe hardening and thickening of the mitral leaflets distinguishes the two diseases.

In one reported case, the pulmonic valve was infiltrated by atheroma.\(^2\) We did not encounter such a patient in the present study.

Relation to the Clinical Data

The narrowing of the aortic root has been presumed to progress with aging, from atherosclerotic findings through autopsy. In the present study, however, this relationship was not demonstrated. The echocardiographic measurements did not indicate the change of the tissue characterization of the aortic wall but the narrowing of the internal diameter of the aortic wall by

![Figure 7. Correlations of serum cholesterol with the normalized internal diameter of the sinus of Valsalva and that of the supravalvular ring. Abbreviations are as in figure 5.](image1)

![Figure 8. Long- and short-axis views of the mitral valve in a homozygote (case 28). The leaflets are thickened and distorted nonuniformly and are partly calcified. The left ventricular wall is hypertrophied due to supravalvular aortic stenosis. IVS = ventricular septum; AML = anterior mitral leaflet; PML = posterior mitral leaflet.](image2)
atheromatous plaque. A noticeable finding in relation to patient age was that the homozygotes without exception showed severe aortic root lesion despite their youth. This finding is well known from autopsy studies.\(^2\) However, the present study demonstrated that the lesion could be visualized noninvasively. It is important to examine the homozygote frequently because the progression of the atheromatous plaquing is rapid even in young patients. We believe that echocardiography is suitable for this purpose.

The close relationship between atherosclerosis and serum cholesterol has been pointed out in epidemiologic studies. In this study, aortic root narrowing correlated definitely with serum cholesterol levels, showing that the atherosclerosis is often so severe that it results in narrowing of the aortic lumen. The reduced murmur of aortic stenosis in homozygotes who have undergone portocaval shunt with a decrease in serum cholesterol level suggests that atheromatous plaquing may be altered by lowering the cholesterol level.\(^8\)\(^,\)\(^9\)

Whereas the internal diameter of the supravalvular ring showed a strong linear correlation to the serum cholesterol level, this was not true of the internal diameter of the sinus of Valsalva. This finding supports the concept, discussed above, regarding the development of the atheromatous plaquing. That is, the higher serum cholesterol level is, the more severely atheromatous plaquing develops, extending from the supravalvular ring to the sinus of Valsalva.

Xanthoma is a visible form of atheroma. Most of the patients with xanthoma also had supravalvular aortic stenosis due to atheroma on the aortic wall. However, the skin lesion and aortic root lesion did not always coexist. We believe that the mechanism of the progression of the atheroma on the skin may be different from that on the aortic root.

Supravalvular aortic stenosis and ostial stenosis of the coronary artery, both of which are fatal complications in familial hypercholesterolemia, could be diagnosed using two-dimensional echocardiography. We conclude that two-dimensional echocardiography can be useful in follow-up treatment and group examination.

References
Supravalvular aortic stenosis and coronary ostial stenosis in familial hypercholesterolemia: two-dimensional echocardiographic assessment.
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_Circulation_. 1983;67:878-884
doi: 10.1161/01.CIR.67.4.878

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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