Left Ventricular Morphometric Estimation of the Coarctation Complex in the First Year of Life

Goki Shindo, M.D., Akira Mizuno, M.D., Akira Ueno, M.D., Masahiro Saigusa, M.D., Minoru Tsunemoto, M.D.,* and Ryozo Okada, M.D.**

SUMMARY

Coarctation complex is a serious congenital cardiovascular malformation in infants. It is associated with severe congestive cardiac overload and high mortality even after surgical treatment.

To investigate left ventricular performance, quantitative morphometry and histometry of the left ventricle were carried out in 19 autopsied patients who died without surgical intervention. The following results were obtained:

1. Coarctation of the aorta was found to selectively affect the left ventricle, showing a volume overload response without effectively adapting to the pressure overload; the right ventricle showed a significant reaction to the pressure overload.

2. The coronary arterioles responded to the pressure load in the left ventricle.

In order to promptly recover left ventricular function, simple coarctectomy without VSD closure or other procedures is advisable for treatment of the coarctation complex in the early months of life.

Additional Indexing Words:
Coarctation complex Hypoplasia of left ventricular outflow tract Total length of heart muscle fibers Thickness index of the ventricle Volume overload Pressure overload

Coarctation complex, frequently complicated by congestive heart failure in early infancy, resists therapy and is consequently associated with a high mortality rate. Surgery still has unsatisfactory survival rates. To improve surgical and medical treatment, morphological and physiological analyses of this anomaly are essential. There have been a few reports

From the Department of Thoracic Surgery, Faculty of Medicine, University of Tokyo, the Department of Cardiovascular Surgery, the National Children's Hospital,* and the Department of Internal Medicine, Juntendo University,** Tokyo.

Address for reprint: Goki Shindo, M.D., Department of Thoracic Surgery, Faculty of Medicine, University of Tokyo, Hongo 7–3–1, Bunkyo-ku, Tokyo 113, Japan.

Received for publication January 31, 1981.
Manuscript revised February 20, 1982.

685
which attempted to decipher the morphometric characteristics of the coarctation complex.

Morphometric and histometric analyses of the coarctation complex in patients who died without surgical intervention were attempted in this study. Morphogenetic factors were also considered.

MATERIALS AND METHODS

1. Materials

Nineteen necropsied infants with the coarctation complex without extracardiac anomalies and/or complicated cardiac anomalies such as Taussing-Bing anomaly, transposition of the great arteries, a single ventricle or hypoplasia of the aortic tract complex9) were studied. Patients with congenital aortic valve stenosis and patients undergoing extracorporeal circulation were excluded. All patients, autopsied during the period from 1968 to 1975 at the National Children’s Hospital, Tokyo, presented with signs and symptoms of severe congestive heart failure and died without surgical intervention due to late detection or severity of condition. Of 19 infants with the coarctation complex (Group A);

(a) 5 (3 males, 2 females; average age 7 months and 14 days) had coarctation of the aorta associated with VSD and pulmonary hypertension (Group A-1),
(b) 6 (4 males, 2 females; average age 1 month and 22 days) had coarctation of the aorta with VSD and patent ductus arteriosus (PDA) (Group A-2),
(c) 8 (3 males, 5 females; average age 2 months and 25 days) had coarctation of the aorta with VSD, PDA, and atrial septal defect (ASD) (Group A-3).

Twenty-two normal hearts (Group C), obtained from infants aged under 1 year dying from causes other than cardiovascular diseases, were examined for comparison. Of these 22 autopsied infants, 14 were males and 8 females; their average age was 4 months and 4 days. The age distribution by month was uniform. A total of 41 hearts were examined.

2. Methods

All patients examined in this study were autopsied 2 to 8 hours after death. The ventricles and atria were opened and fixed in 4% formaldehyde. Special techniques such as ventricular and atrial pressure fixation10) were not performed.
(1) Macroscopic measurement of the heart

Atrial volume was calculated using the formula for a sphere. Right ventricular volume was calculated as the sum of two cones representing the outflow and inflow portions of the right ventricle. Left ventricular volume was calculated as an inverted cone. Right ventricular wall thickness was measured by the method of Lev\textsuperscript{11}; the widths of the substantia compacta at three points—the outflow portion, the inflow portion, and the apex of the right ventricle—were added to derive the right ventricular thickness index (t-RV Index). Left ventricular wall thickness was measured by a modification of the method of Okada\textsuperscript{12}; the same three points as in the right ventricle were measured and added to derive the left ventricular thickness index (t-LV Index).

To minimize intersubject variations, measurements were corrected using individual body surface areas (BSA)\textsuperscript{13},\textsuperscript{14}, i.e., chamber volumes were divided by $\sqrt{\text{BSA}}^3$, and valve areas were divided by BSA. Ventricular wall thickness was divided by $\sqrt{\text{BSA}}^3$ to derive the wall thickness mass index.

(2) Histometric measurement of the myocardium

Several blocks of myocardium were sectioned vertically and horizontally from the outflow and inflow portions of each ventricle. The blocks were fixed in 4% formaldehyde, embedded in paraffin, sliced into $6\mu$ sections, and stained with hematoxylin-eosin or elastica-Van Gieson's stain. Histometric measurements of myocardial fiber diameter (Dd) were carried out by Chalkley's method\textsuperscript{15},\textsuperscript{16} and the total myocardial fiber length (Lm) of each ventricle was measured by Suwa's method.\textsuperscript{17} Before calculation of Lm, myocardial fiber weight (W) of each ventricle was measured from the ventricular mass index according to the methods of Rimoldi and Lev\textsuperscript{18} and the specific gravity of the myocardium was determined as described by Masshoff et al.\textsuperscript{19} The capacity of ventricular heart muscle fibers (Wm) was obtained by dividing W by the specific gravity of the myocardium.

The thickness of the media (D) and the radius (R) of coronary arterioles ($R<100\mu$) was measured by Suwa's method. Specimens of the myocardium were examined under a light microscope (1,000X) and photographed.

The length of the inner elastic layer (L) of horizontally sectioned arterioles and the area between the internal and external elastic layers (S) were measured with a pranimeter.

The radii (R) of the arterioles, the distances between the center of the lumen and midpoint of the media in diastole, and the widths of the media (D) of arterioles under the same conditions were calculated by the following formulae:
The correlation of and differences between measurements were statistically analyzed by the method of Rowlatt, Rimoldi, and Lev.\textsuperscript{14,20} \(P<0.05\) was used as the level of significance.

**RESULTS**

1. Macroscopic measurements of the heart

(1) The volume indices of the right atrium (v-RA), left atrium (v-LA), right ventricle (v-RV), and left ventricle (v-LV), collected by \(\sqrt{\text{BSA}}\), are summarized in Table Ia.

Volume indices were significantly higher in the coarctation complex groups than in the normal heart group (\(p<0.05\)–\(0.01\)). The v-RA/v-LA ratio (Table Ia) was lower in subgroups A-1 and A-2, indicating a significant

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<th>Table I. Morphometry of the Coarctation Complex</th>
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<tr>
<td>a. The Volume Index:</td>
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<tr>
<td>RA (v-RA/BSA(^{3/2})(cm(^{3})/m(^{2}))</td>
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<tr>
<td>LA (v-LA/BSA(^{3/2})(cm(^{3})/m(^{2}))</td>
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<tr>
<td>RV (v-RV/BSA(^{3/2})(cm(^{3})/m(^{2}))</td>
</tr>
<tr>
<td>LV (v-LV/BSA(^{3/2})(cm(^{3})/m(^{2}))</td>
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<tr>
<td>Ratio of RV and LV volume index:</td>
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<tr>
<td>(\frac{v-RV}{v-LV})</td>
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<tr>
<td>b. The Wall Thickness Index:</td>
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<tr>
<td>RV (t-RV/BSA(^{1/2})(cm(^{3})/m(^{2}))</td>
</tr>
<tr>
<td>LV (t-LV/BSA(^{1/2})(cm(^{3})/m(^{2}))</td>
</tr>
<tr>
<td>Ratio of RV and LV:</td>
</tr>
<tr>
<td>(\frac{v-RV}{v-LV})</td>
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\(*p<0.05, \quad **p<0.01.*

Table I shows the mean±SD of the volumes of atria and ventricles in Panel a and the wall thickness of both ventricles of each group in Panel b.
increase in left atrial volume. The v-RA/v-LA ratio in Group A-3 was comparable to that of normal hearts. There was a high correlation \((r=0.8)\) between v-RV and v-LV in each group.

(2) The wall thickness indices of the right ventricle (t-RV) and left ventricle (t-LV), divided by \(\sqrt{BSA^3}\), are shown in Table Ib for each group.

The coarctation complex group showed notable differences in wall thickness compared with normal hearts. In correlation between t-RV and t-LV, t-LV showed a remarkable increase compared with t-RV in normal hearts. In the coarctation complex group, on the other hand, t-RV showed a remarkable increase compared with t-LV (Fig. 1). These results indicate a poor response of the left ventricle to the pressure overload compared with the right ventricle, in spite of a good response to the volume overload.

The aortic valve area and the cross sectional area of the ascending aorta in the coarctation complex group did not differ significantly from the normal heart group.

2. Histometric measurement of the heart

(1) The diameters of ventricular muscle fibers (Dd) were measured in
Fig. 2. The diameters of muscle fibers (Dd) of the left and right ventricles were measured by Chalkley's method. The coarctation complex group did not show a significant increase compared with normal hearts in the left ventricle.

Fig. 3. The total length of muscle fibers (Lm) was measured by Suwa's method. The ordinate shows the total length of muscle fibers (Lm), and the abscissa muscle capacity (Wm). The coarctation complex group, shown in line 3, showed the same growth rate of LV muscle fibers as normal hearts, shown in line 1.
cross section. Group A-2 showed remarkable increases in Dd in the right ventricle compared with normal hearts (Fig. 2), but there was no significant difference between Group A-1 and the normal heart group. In the left ventricle, however, there was no significant difference in Dd between the coarctation complex group and the normal heart group. This fact corresponded to the poor response of the left ventricular wall thickness against the pressure load. It is of interest that in some cases of Group A-2, Dd of the left ventricle was found to be smaller than that of normal hearts (Fig. 2), suggesting the presence of cardiac failure in these cases.

(2) In the coarctation complex group the total length of muscle fibers (Lm) of the left ventricle increased at the rate of $\sqrt{W^3}$ (Fig. 3). That is, the

![Graph showing the ratio between the width of the media (D) and the radius of coronary arterioles (R) for different groups.](image)

Fig. 4. The ratio between the width of the media (D) and the radius of coronary arterioles (R) showed a significant increase in the coarctation complex group. This was attributed to an independent response to the pressure overload in the coronary artery system of patients with the coarctation complex.
growth rate of muscle fibers in the coarctation complex was comparable to that of normal hearts.

The right ventricle also showed nearly the same rate of increase as the left ventricle. Line 1 in Fig. 3 shows the Lm-Wm recurrent curve in normal hearts and line 3 is of the coarctation complex group. These results indicate an effective response of the left and right ventricles to the volume overload.

(3) Although there was no significant difference between Group A-1 and normal hearts, the ratio between the width of the media (D) and the radius (R) of coronary arterioles less than 100μ in diameter showed a significant increase (p<0.01) in Group A-2 (Fig. 4). These results indicate an effective response of coronary arterioles of the coarctation complex group to the pressure load caused by coarctation of the aorta.

(4) The total length of capillaries per cubic centimeter of myocardium (Lc/Wm) is shown in Fig. 5. The coarctation complex group showed an exponential curve similar to that of normal hearts, i.e., as the capacity of heart muscle (Wm) increased, Lc/Wm decreased exponentially and reached a constant value at about 10 cm³ of the myocardial capacity. This means that after this point muscle fibers and capillary length increase at the same rate. There is, therefore, no lack of capillary supply in these circumstances.

DISCUSSION

DeBoer and Lev⁸³ used the term "coarctation complex" for the first time to designate coarctation of the aorta in fetal cases. According to their definition the fetal coarctation complex is characterized by anomalies which cause a narrowing of the aorta proximal to the ductus arteriosus, associated with right ventricular hypertrophy related to pulmonary hypertension, and
hypoplastic left heart, although they did not describe these cardiac anomalies in detail. In this study, the authors used the term "coarctation complex" in a somewhat extended sense, meaning coarctation of the aorta associated with other cardiac anomalies.

Some problems in morphometric measurement should be mentioned. First, contraction and degeneration of the heart muscle in autopsied cases results from rigor mortis and fixing with formaldehyde. In all cases studied in this paper no special measures were taken to avoid rigor mortis. According to Friedman, the mean volume of autopsied hearts was only 67% of the volume in systole measured by angiocardiography; his findings demonstrated that a heart treated with formaldehyde weighed considerably less than previously reported. Based on these facts, measurements obtained in this study cannot be directly correlated to living cardiac conditions. It is, however, acceptable to compare cases and groups with each other, because all subjects were selected at random from one hospital and were treated with the same pathological procedures.

Second, the authors adopted the mass index method devised by Rimoldi and Lev to measure the weight of the ventricular muscle. The weight of free wall of the ventricle, excluding the septum, is obtained by this method. Weights measured by this method are lighter than those obtained by Lewis' method. The correlation between measurements by Lev's method and those by Suwa's method was high (r=0.95); good correlation was also obtained between Lev's method and Recavarren's method (r=0.98). Ventricular weight calculated by the method of Rimoldi and Lev was found to be the most suitable, because in this study samples of heart muscle were taken from the free wall of the ventricles.

Lev elucidated morphologic changes in heart muscle resulting from volume load and pressure load on the heart and he defined the term "hypertrophy of ventricles" as an increase in the muscle mass of the parietal wall. In the absence of such measurements, a ventricle is presumed to be hypertrophied if the thickness index increases while the volume index remains normal. "Pressure hypertrophy" is defined as the presence of hypertrophy when the volume index is found to be normal. "Volume hypertrophy" is defined as the presence of hypertrophy without heart failure, i.e., the volume index increases, while the thickness index remains normal. From the viewpoint of histometry, "pressure hypertrophy" is defined as the increase in diameter (Dd) of a cross section of muscle fibers of the ventricles, while the total length of muscle fibers (Lm) of the ventricles remains within normal range. "Volume hypertrophy" is defined as the presence of hypertrophy with an increase in the total length of muscle fibers, while the diameter of muscle fibers remains
within normal range.

No direct measurements of the distance between the Z-bands, i.e., the length of one sarcomere, were made in this study. According to Linzbach,\textsuperscript{24}) there is no significant difference in the length of a sarcomere in either concentric hypertrophy, eccentric hypertrophy, or myocarditis. From the viewpoint of electron microscopy, "hypertrophy" is defined as a reaction to sarcomere increase.

In the coarctation complex, left and right ventricles showed apparent different morphological responses to pressure and volume loads in this study. A sufficient response to the volume overload without an effective response to the pressure overload, observed selectively for the left ventricle, is specifically characteristic of coarctation of the aorta. On the other hand, the right ventricle showed a significant reaction to the pressure overload.

Hypertrophy of the right ventricle is produced by pulmonary hypertension which may be induced by considerable left to right shunt. This increase in shunt may be caused by a small left ventricle combined with a relatively large ventricular septal defect, especially when severe coarctation of the aorta disturbs blood flow from the left ventricle to the extremities. Thickening of the media without intimal thickening of coronary arterioles against the pressure overload suggests a high safety margin of the coronary arterial system.

There was a different response to the same pressure load between the muscular system and the vascular system in the same heart. Coarctation of the aorta with VSD-PDA (Group A-2) showed marked thickening of the media of coronary arterioles against the pressure load. Systemic systolic blood pressure in this group was 1.38 times higher than that of normal hearts. There was, however, no increase in the diameter of left ventricular muscle fibers in reaction to the same pressure load. This may be explained by the fact that each system plays different roles, i.e., the ventricular myocardium supplies blood to the entire body to meet the oxygen demands of all organs, whereas the coronary arteries supply blood to the heart alone. There may be another explanation for the difference in response between muscle fibers and coronary arteries. Myofibrils of the left ventricle are originally smaller in the coarctation complex than in normal hearts, so that their diameter remains smaller even after growth and development of the heart under the same pressure overload. This fact suggests the existence of a genetic handicap for left ventricular muscle fibers in the coarctation complex.

In conclusion, the aforementioned findings clearly indicate that simple coarctectomy should be undertaken in early infancy before the onset of irreversible changes in the myocardium and coronary arteries. This procedure will hopefully improve left ventricular function and increase patient sur-
vival. A recent report by one of the authors seems to support our conclusion.

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