Left Ventricular Function in Children
Studied by Increasing Peripheral Resistance
with Angiotensin

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SUMMARY
Response to angiotensin infusion was evaluated in 11 normal children and 24
patients with suspected left ventricular dysfunction. This included 12 patients with
endocardial fibroelastosis, three with idiopathic myocardial hypertrophy, one with
cardiac glycogenosis, and eight with the Hunter-Hurler syndrome. In 20 of these 24
patients, cardiac catheterization findings confirmed the clinical suspicion of decreased
left ventricular function. In 11 instances left ventricular dysfunction was diagnosed by
an elevation of resting left ventricular end-diastolic pressure. In eight instances this
was ascertained by a decrease in resting left ventricular stroke work when compared to
the expected range, derived by using a linear regression formula based on 24 normal
subjects. In only four instances were both abnormal; that is, the resting left ventricular
stroke work was decreased and the left ventricular end-diastolic pressure was increased.
In five of these 20 patients, abnormal left ventricular function was elicited only on
infusion of angiotensin. Thus this test is a significant adjunct in our ability to de-
termine myocardial malfunction at cardiac catheterization.

Additional Indexing Words:
Stroke work Hunter-Hurler syndrome Endocardial fibroelastosis
Cardioglycogenosis Idiopathic myocardial hypertrophy

WHILE cardiac catheterization and selective angiocardiography are satisfac-
tory techniques for the detection of shunts and the evaluation of mechanical function of
heart valves, assessment of myocardial function remains difficult. In many instances,
cardiac catheterization findings in patients with endomyocardial disease have been most
disappointing, beyond determining the presence or absence of heart failure. Both left
ventricular end-diastolic pressure, which when elevated leads to left atrial and pulmonary
hypertension, and cardiac output reflect the severity of the heart failure.1 Cardiac catheter-
ization has been particularly disappointing in the group variously labeled as idiopathic
myocardial hypertrophy or cardiomyopathy, unless associated with hypertrophic obstruc-
tion of the left ventricular outflow tract.2

Sancetta3 and Yu and co-workers4 demonstrated in normal human subjects that the
pressor agent, angiotensin, produced an increase in left ventricular stroke work by
augmenting resistance to ventricular ejection, with a corresponding increase in pulmonary
artery wedge pressure. Ross and Braunwald,5 using graded infusions of angiotensin, studied
18 patients with and without clinical evidence of impaired left ventricular function. These
patients were separated into three groups: (1)
a control group of six subjects, ranging in age from 13 to 37 years, (2) six patients whose left ventricular function curves were markedly depressed, and (3) a group of six patients whose left ventricular function lay between the above groups. One control subject had an innocent murmur, two had minimal pulmonic valvar stenosis, one had had surgical correction of a valvar pulmonic stenosis 2 months prior to study, and two had inactive rheumatic heart disease with pure mitral stenosis.

Because of the potential importance of this procedure, it was deemed worthy to extend this study to children. Included in the present report are 11 control subjects with normal left ventricular function, as well as 24 patients with suspected left ventricular dysfunction including 12 with endocardial fibroelastosis, one with glycogen storage disease of the heart, eight with the Hunter-Hurler syndrome, and three with idiopathic myocardial hypertrophy. More detailed hemodynamic information on our patients with endocardial fibroelastosis6 and the Hunter-Hurler syndrome7, 8 has been reported previously.

Methods

The 11 children who constituted the “normal” controls for this paper were catheterized either for evaluation of surgical closure of a secundum atrial septal defect or because of difficulty in determining the significance of unusual clinical, ECC, or x-ray findings. In all of the cases of atrial septal defects, these defects were judged successfully closed by hydrogen electrode technique, and no evidence of significant heart disease was found in any of these 11 children.

Consent for these procedures was obtained from the parents after the general outline of the study had been approved by the Health Center Committee on Human Investigation.

All patients were studied in the postabsorptive state and had received a single intramuscular dose of 1 mg/kg of meperidine, 0.25 mg/kg of promazine hydrochloride, and the same amount of chlorpromazine hydrochloride. Left ventricular pressure was measured by retrograde arterial catheterization in all patients. Cardiac output was determined by indicator-dilution techniques including computer calculation of the cardiac outputs.9 Left ventricular stroke work was calculated using the following formula:

Left ventricular stroke work = SV \times (SAM - LVEDP) \times 1334 \div 10^7 \text{ in which } SV = \text{ stroke volume in milliliters,}
SAM = \text{mean systemic arterial pressure, and}
LVEDP = \text{left ventricular end-diastolic pressure.}

Stroke work is calculated in Newton-meters, which is the equivalent of force times distance.

After base-line duplicate determinations of cardiac output, and mean systemic arterial and left ventricular end-diastolic pressures were obtained, intravenous infusion of angiotensin was begun. The infusion rate varied from 0.2 \mu g to 3.8 \mu g/min. Infusion was usually begun at 0.38 \mu g/min, although in the smaller patients the initial step was one half of this value. The infusion rate was approximately doubled at 2 to 3-min intervals until an elevation of left ventricular end-diastolic pressure of between 5 and 10 mm Hg was obtained in association with a distinct arterial pressure response. Correlation of the rate of angiotensin infusion needed for adequate pressure response with body size was poor. Fortunately, it is simple to determine an adequate infusion rate empirically. If the initial infusion rate proves inadequate, the amount is increased. If, however, left ventricular end-diastolic pressure should rise more than 10 mm Hg with the initial infusion, the rate should be reduced promptly. It is neither necessary, nor particularly desirable, to increase left ventricular end-diastolic pressure higher than this. As emphasized by Goodman and Gilman,10 the greatest danger in the use of this drug lies in its powerful pressor activity: “too rapid infusion may easily raise blood pressure to alarming levels.” Fortunately, the duration of the angiotensin response is extremely brief,4 and patients stabilize within a minute or two to a new level of angiotensin infusion. Our initial experience sometimes resulted in more than the desired or anticipated elevation of left ventricular end-diastolic pressure (see fig. 3, cases 5, 9, and 11). These observations emphasized the need for close observation during the administration of angiotensin to prevent an excessive load on the left ventricle. When the proper rate of angiotensin infusion is found, cardiac outputs and the indicated pressures are again measured.

Following cessation of the infusion, pressures rapidly returned to normal and reached control values within 2 to 5 min. Mild hypotension has

*We prefer to use Newton-meters, from the meter-kilogram-second (MKS) system rather than either gram meters or kilogram meters. This avoids confusion over the use of gram mass versus gram weight and also avoids using a hybrid from both centimeter-gram-second (CGS) and MKS systems. Use of dyne-centimeters is also proper, but results in very large numbers.
## Table 1

**Response of Control Subjects to Infusion of Angiotensin**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>Pressures (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Heart rate</th>
<th>Stroke vol (ml)</th>
<th>Stroke work (Newton-m)</th>
<th>Diagnosis</th>
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<tr>
<td></td>
<td></td>
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<td>M</td>
<td>110</td>
<td>18</td>
<td>72</td>
<td>7</td>
<td>4.3</td>
<td>68</td>
<td>63</td>
<td>0.54 Innocent</td>
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<td>18</td>
<td>56</td>
<td>3</td>
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<td>21</td>
<td>73</td>
<td>9</td>
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<td>0.31 Postop.*</td>
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<td>34</td>
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<tr>
<td>9</td>
<td>11.8</td>
<td>F</td>
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<td>37</td>
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<td>9</td>
<td>5.5</td>
<td>78</td>
<td>71</td>
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<tr>
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<td>78</td>
<td>62</td>
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<tr>
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<td>29</td>
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</table>

*All had surgically corrected secundum atrial septal defects and have normal pressures and no residual shunts.

ASD = atrial septal defect; PA = pulmonary artery; LVEDP = left ventricular end-diastolic pressure.
been observed following the discontinuation of infusion of angiotensin in older patients, but has not occurred in any patients in this series. A few patients complained of headaches and nausea during the highest rate of angiotensin infusion. An increased number of premature ventricular contractions due to the stimulation of the catheter in the left ventricle during angiotensin infusion was frequently seen, but subsided promptly with cessation of the infusion. There were no instances of chest pain, significant electrocardiographic abnormalities, or other complications as a result of such studies.

The normal value of left ventricular stroke work (LVSW) was predicted using a linear regression formula based on 24 normal subjects. The formula is: 

$$LVSW = 0.745 + 0.0133 \times wt \ (kg) - 0.00243 \times ht \ (cm) - 0.00384 \times \text{heart rate.}$$

**Results**

The hemodynamic effects of angiotensin infusion in 11 normal subjects are illustrated in table 1. Five of the patients were catheterized following surgical closure of a secundum atrial defect. They were included in this study since they had no residual left-to-right shunt as determined by hydrogen electrode and had normal right heart pressures. Patient 6 had minimal aortic stenosis with a left ventricular-aortic root systolic pressure difference of 18 mm Hg. Patient 11 had a chromosomal abnormality (XXXXY) and severe pectus excavatum. The remaining four patients had no evidence of significant heart disease, although some variety of congenital heart disease had been suspected prior to catheterization because of an unusual murmur, x-ray or electrocardiogram. The ages of these normal subjects varied from 5 to 14 years, and the group included four females and seven males. Left ventricular function curves of this group are shown in figures 1 and 2.

Left ventricular function curves are shown in figure 1 as plotting the left ventricular end-diastolic pressure (LVEDP) against the left ventricular stroke work (LVSW) index. The four normal children included in the Ross and Braunwald series are also shown in this figure. With the exception of a slightly greater spread of the normal range with the inclusion of more subjects, values are similar to those found by Ross and Braunwald.

Earlier doubts concerning the validity of using body surface area as normalizing factor for cardiovascular functions led us to use regression equations to predict normal values for patients of various sizes. Results using this technique are illustrated in figure 2. LVEDP is plotted against the observed LVSW divided by the LVSW predicted by the regression equation. The normal resting range as obtained in 24 children is illustrated in the shaded portion. This technique offers a slightly narrower range for normal changes following angiotensin infusion, as well as better definition of the resting normal range than the other one. For example, patient 2 (fig. 3) was within the normal range when considered on the stroke work index basis, although the response to angiotensin is clearly abnormal.
Hemodynamic effects of angiotensin infusion in 11 normal subjects. The left ventricular function curves in this and the subsequent figures were calculated as the observed (that is, actually measured) left ventricular stroke work divided by that predicted by a regression equation. This method of plotting has the advantages of first offering a narrower normal range than that used for figure 1 and secondly avoiding the controversial use of body surface area as a normalizing function.\textsuperscript{11, 12} In all of these figures, number 1 is the youngest patient in each series and the numbering is according to chronological age.

The results of stress from angiotensin in 12 patients with endocardial fibroelastosis are shown in figure 3. Four patients (nos. 2, 6, 10, and 12) had elevated LVEDP even prior to the infusion of angiotensin. Thus, the presumption of an abnormal left ventricular function was obvious from pressure measurements alone. Similarly, four patients (nos. 1, 3, 5, and 8) had a resting LVSW below the normal limits for this laboratory. A presumption of abnormal left ventricular function could also have been made in these eight patients without resorting to infusion of angiotensin. Note, however, that the remaining four cases (nos. 4, 7, 9, and 11) each had a rise in LVEDP and LVSW well within the normal range. When stressed with angiotensin, LVSW fell with a rise in LVEDP in patient 4; LVSW rose slightly and then fell in patients 7 and 11, and in patient 9, the rise in stroke work was less than normal for the magnitude of the LVEDP increase.

The response to angiotensin infusion in three patients with idiopathic myocardial hypertrophy is shown in figure 4. Of these, patients 2 and 3 had markedly elevated left ventricular end-diastolic pressures at rest. Patient 1 had borderline elevation of the LVEDP (12 mm Hg). The diagnosis of left ventricular dysfunction in this 5-year-old girl was clearly established by angiotensin infusion. Patient 2, in spite of a resting left ventricular end-diastolic pressure in the normal range, showed a marked rise in LVEDP with angiotensin. However, the rise in LVSW was much less than normal, suggesting that the ventricular dysfunction was mild.
Hemodynamic effects of angiotensin infusion in three patients with the clinical diagnosis of idiopathic myocardial hypertrophy. Patients 2 and 3 had markedly elevated LVEDP. Patient 1 had an LVEDP of 12 mm Hg, but a diagnosis of left ventricular dysfunction was clearly established by the lack of an increased LV stroke work in the presence of an increased LVEDP.

A ventricular end-diastolic pressure of 17 mm Hg, was able to increase her left ventricular stroke work at nearly a normal rate.

Figure 5 illustrates the response to angiotensin infusion of a 2-month-old white, male child with cardiac glycogenosis. The resting left ventricular end-diastolic pressure, 10 mm Hg, intriguingly was within our normal limits. In contrast, he had the lowest resting left ventricular stroke work ever recorded in this laboratory, only 18% of expected normal. Following infusion of angiotensin, it decreased further to 14% of the predicted value.

Serious cardiovascular disease is an established hazard in patients with lipochondrodystrophy (Hunter-Hurler syndrome).

Over half of these patients die in congestive heart failure or in ways suggesting cardiac disease. The actual disease process has been thought to be coronary artery disease, valve deformities, as well as endocardial fibroelastosis, generalized arterial disease, and myocardial involvement. In earlier studies in this laboratory, we noted systemic hypertension, but were unable to find any evidence of either significant valve involvement, congenital heart disease, or coronary artery disease. This suggested to us that the postulate of Beebe and Formel that death was often due to myocardial involvement warranted further investigation.

The results of angiotensin infusion in eight patients with Hunter-Hurler syndrome are shown in figure 6. Four of these tests were distinctly abnormal (1, 4, 6, and 7) and indicate that the left ventricle does not function

Figure 4
Hemodynamic effects of angiotensin infusion in three patients with the clinical diagnosis of idiopathic myocardial hypertrophy. Patients 2 and 3 had markedly elevated LVEDP. Patient 1 had an LVEDP of 12 mm Hg, but a diagnosis of left ventricular dysfunction was clearly established by the lack of an increased LV stroke work in the presence of an increased LVEDP.
Hemodynamic effects of angiotensin infusion in eight patients with the Hunter-Hurler syndrome. Four of these patients had distinctly abnormal responses and left ventricular function curves. This confirms our previous notion\(^7\), \(^8\) that these patients often have cardiomyopathy.

normally. These data conclusively established that patients with the Hunter-Hurler syndrome commonly have an abnormal myocardial response to stress.

**Discussion**

Angiotensin is a powerful peripheral arteriolar constrictor, capable of causing profound systemic hypertension. Such increases in arterial pressure in both animals and humans having an intact baroreceptor response slow the heart rate\(^14\) (fig. 7). Our initial consideration was that the decreased heart rate, by shifting the patient to a different ventricular function curve, might defeat the use of the angiotensin test. Berglund and associates\(^15\) showed in dogs that changes from a rate of 43/min to 100/min caused about a 15% decrease in left ventricular stroke work at any given left ventricular end-diastolic pressure. Further increases to 240/min caused inversely proportional decreases in left ventricular stroke work at comparable levels of left ventricular end-diastolic pressure. In contrast, Covell and associates\(^16\) found that increasing heart rates improved ventricular function. For the intact human heart, Sonnenblick and associates\(^17\) found that the force of contraction changed little even with large alterations in rate.

In our studies, fortunately, changes in heart rates were found to be less than 20/min in 22 of our 31 patients. While changes in heart rate in the remaining nine may have caused errors in estimating left ventricular function, we estimate that this was not of such magnitude to negate use of this technique in differentiating degrees of myocardial function. If we apply Berglund's data, the magnitude of this error should be less than 5% for a change of heart rate of 20
beats/min. In any event, there was no correlation between heart rate change and left ventricular function curves in the present study.

The ages of the normal controls ranged from slightly less than 5 to 14 years, while the patients with suspected left ventricular dysfunction were slightly younger. Fourteen of this latter group were under 5 years of age, and five were less than 1 year old. While we have no reason to suspect that left ventricular function would be markedly different for children younger than our control group, this discrepancy in ages of the control and abnormal groups remains as a weak point in our argument.

Abnormal left ventricular function can be determined in one of three ways: (1) an increased resting left ventricular end-diastolic pressure, (2) a resting left ventricular stroke work less than normal, or (3) a less than normal increase in left ventricular stroke work for a given increase in left ventricular end-diastolic pressure following angiotensin infusion or exercise. When left ventricular stroke work remains constant or even decreases with increasing left ventricular end-diastolic pressure, the test is clearly abnormal. We think it likely that, as in other biological phenomena, there is an intermediate group where stroke work rises but at a rate lower than that found with more normal left ventricular function. We have indicated the range of the normal rate of increase in left ventricular stroke work as dashed lines in the figures. Since this is based on a small sample of only 11 subjects, the exact slope of these lines will probably change with further experience. Fortunately, borderline tests are not common. At most, four of our patients fall into this category. Patient 9 of figure 3 was considered abnormal because his stroke work increased at only two thirds the expected minimum, while patients 2, 3, and 5 of figure 6 were considered to be on the low side of normal. In only one of the 20 subjects with left ventricular dysfunction during angiotensin stress was the test even possibly borderline.

A more serious criticism of the method concerns patients with endocardial fibroelastosis. Mitral insufficiency is a common accompaniment of this disease. Since total stroke volume is not measured by these techniques, the test would be invalid in the presence of significant degrees of mitral regurgitation. Selective left ventricular angiograms were performed in 10 of the 12 patients with endocardial fibroelastosis. Three of these (patients 4, 6, and 12) had definite but moderate mitral insufficiency while three others had questionable mitral insufficiency (patients 1, 3, and 8). A competent valve was found in patients 5, 9, and 11. While increasing systemic resistance might be expected to increase the degree of mitral insufficiency, there were no differences in the response to angiotensin of these three groups.

It might be asked, why not obtain left ventricular function curves by exercise as is commonly done in adults? The answer to this lies in the age distribution as outlined above. Few of these patients were old enough and cooperative enough to exercise with several

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total subjects</th>
<th>Abnormal LV function</th>
<th>Increased resting LVEDP</th>
<th>Decreased resting LVSW</th>
<th>Both</th>
<th>Only abnormal by response to angiotensin</th>
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<td>12</td>
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<td>0</td>
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<td>4</td>
<td>3</td>
<td>1</td>
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<td>Total</td>
<td>24</td>
<td>20</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>5</td>
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</tbody>
</table>

KEY: LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVSW = left ventricular stroke work.
cardiac catheters in place.

The value of these tests is illustrated in table 2. Of 24 subjects with suspected abnormal left ventricular function prior to catheterization, 20 proved to have left ventricular dysfunction.

In only 11 of these was the dysfunction confirmed by an increased resting left ventricular end-diastolic pressure (table 2). The inadequacies and errors in using this as a sole criterion of left ventricular function have been pointed out previously by Braunwald and associates. In eight of our patients, four of whom also had increased left ventricular end-diastolic pressure, resting left ventricular stroke work was below normal limits for this laboratory. In five, the only indication of abnormal left ventricular function was obtained with infusion of angiotensin. Thus, in 25% of the subjects with left ventricular dysfunction, this was detected only by increasing the left ventricular outflow resistance with angiotensin.

References
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L. JEROME KROVETZ, THOMAS G. MCLoughlin and GEROLD L. SCHIEBLER

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