Studies on Digitalis

V. Comparison of the Effects of Ouabain on Left Ventricular Dynamics in Valvular Aortic Stenosis and Hypertrophic Subaortic Stenosis

By Eugene Braunwald, M.D., Edwin C. Brockenbrough, M.D., and Robert L. Frye, M.D.

The acute hemodynamic effects of digitalization in patients with congestive heart failure have, in the past, been investigated primarily by the technic of right heart catheterization. These studies have permitted a description of the circulatory changes in patients in whom the primary abnormality involves the pulmonary circulation and the right side of the heart. Since the pressures measured at right heart catheterization reflect left ventricular dynamics only indirectly, however, catheterization of the left side of the heart is required to provide a more direct assessment of the changes produced by digitalis glycosides in patients whose disease primarily involves the left side of the heart.

The purpose of the present investigation was to determine the acute circulatory changes produced by a rapidly acting cardiac glycoside, ouabain, in patients with valvular aortic stenosis and in patients with idiopathic hypertrophic subaortic stenosis. These studies were designed to answer three questions: 1. Does this drug have a beneficial or deleterious hemodynamic effect in these two conditions? 2. Can the acute hemodynamic effects of digitalization be used to distinguish between valvular and hypertrophic subaortic stenosis? 3. Can the acute hemodynamic response to digitalization further elucidate the mechanism of the obstruction in patients with hypertrophic subaortic stenosis?

Patient Material

Group I: Valvular Aortic Stenosis

The six patients with valvular aortic stenosis studied ranged in age from 17 to 55 years, with an average of 39 years; all six were men. Three were asymptomatic, while the others had mild to moderate limitation of activity. None was in congestive heart failure at the time of study, but one patient, J.D., had experienced two episodes of acute left ventricular decompensation 1 year earlier. Five patients had no clinical or hemodynamic evidence of other valvular involvement, and the sixth patient, R.R., had a moderate degree of associated aortic regurgitation. All six patients were in sinus rhythm and had electrocardiographic evidence of left ventricular hypertrophy. There was varying degree of left ventricular enlargement on roentgenographic examination in all six patients, and on fluoroscopy all but one (J.O.) exhibited calcification in the region of the aortic valve. The peak left ventricular-brachial artery pressure gradients ranged from 74 to 159 mm. Hg (average 94 mm. Hg) prior to digitalization. Three patients were operated upon and in two (J.O. and C.S.) the valvular stenosis was considered to be congenital in origin; J.D. had a densely calcified and fused valve (table 1).

Group II: Idiopathic Hypertrophic Subaortic Stenosis

The four patients with this lesion ranged in age from 21 to 45 years; three were male and one was female. In every instance the diagnosis was clear from clinical examination, since these patients presented all the features characteristic of this condition. Patients P.S. and M.W. were siblings and the diagnosis of hypertrophic subaortic stenosis had been proved at postmortem examination in one of their sisters. The other two patients had no known familial incidence of heart disease. One patient (T.S.) was asymptomatic; two patients (B.G. and P.S.) complained of mild fatigability and dyspnea, while M.W. was severely limited and had been in overt congestive heart failure during pregnancy. All four patients were in sinus rhythm, had evidence of left ventricular hypertrophy on the electrocardiogram, and they all had moderate enlargement of this chamber on roentgenographic examination. A subvalvular pressure gradient ranging from 20 to 58 mm. Hg was present in all four patients, and selective angiocardiography, carried out in three patients, demonstrated systolic narrowing of the left ventricular outflow tract. The systemic arterial pulse pressure declined in a

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paradoxical manner following a ventricular premature contraction in all four patients.11

Methods
The patients were all studied under basal conditions in the postabsorptive state. Following right heart catheterization through the right saphenous vein, transseptal left heart catheterization was carried out as described elsewhere.12 Prior to digitalization, pressure was measured simultaneously in the left ventricle and brachial artery two or three times at 5-minute intervals and cardiac output was determined, generally in duplicate. Ouabain (0.50 to 0.75 mg) was then injected into the left ventricle over a period of 5 to 10 minutes. Left ventricular and brachial artery pressure measurements were carried out at 10-minute intervals for a period of 50 to 60 minutes; at the end of this period cardiac output was remeasured, again usually in duplicate. Left atrial pressure was measured through the transseptal needle prior to digitalization, and this measurement was repeated after digitalization and the withdrawal of the catheter from the left ventricle.

Cardiac output was measured by the indicator-dilution technic by injecting indocyanine dye into the left ventricle and recording a dilution curve from the brachial artery. A cuvette densitometer13 and motor-driven syringe were employed. In a previous series of 20 duplicate determinations of cardiac output by this technic in this laboratory, the standard error was 6 per cent of the mean value.14,15 Pressures were measured with Statham P23D transducers and were recorded together with the electrocardiogram on a multichannel photographic oscilloscopic recorder.

Results
Group I: Valvular Aortic Stenosis
The left ventricular end-diastolic pressure did not change significantly in two of the patients (R.R. and J.O.) and declined slightly (2 to 5 mm. Hg) in the others. The mean left atrial pressure was recorded before and after ouabain administration in five patients, in three of whom it declined slightly (2 to 4 mm. Hg) while it remained essentially unchanged in the other two patients (C.B. and R.R.). The left ventricular peak systolic pressure rose in all six patients and in four of them (R.R., R.K., C.B., and J.O.) the bra-
chial artery systolic pressure also rose. In one patient (R.R.) the peak systolic pressure gradient showed little change (+4 mm. Hg) while in the other five patients the gradient increased moderately (11 to 35 mm. Hg). Cardiac output was measured in 4 of these 6 studies; a significant increase occurred in J.D. and R.R. (50 and 53 per cent). There was little change in C.B. (+7 per cent) and a slight decline occurred in R.K. (−19 per cent) (table 2, figs. 1 and 2).

**Group II: Hypertrophic Subaortic Stenosis**

Ouabain resulted in an increase of the left ventricular end-diastolic pressure in all four patients with hypertrophic subaortic stenosis. These increases ranged from 6 to 16 mm. Hg, with an average rise of 10 mm. Hg. The mean left atrial pressure also rose by 5 to 9 mm. Hg in the three patients in whom it was recorded. The peak left ventricular systolic pressure rose significantly in all four patients (+14, +23, +28, and +51 mm. Hg) while the brachial artery systolic pressure fell in one patient (P.S., −15 mm. Hg), remained unchanged in one patient (M.W.), and rose in the other two patients. The peak systolic pressure gradients rose significantly in all four patients (+10, +14, +34, and +43 mm. Hg).

The cardiac output fell in two patients (M.W. −25 per cent, B.G. −23 per cent), and remained unchanged in the other two (table 3, figs. 3-6).

**Discussion**

Many of the acute hemodynamic effects of digitalization in subjects with normal cardiovascular systems16, 17 and various types of heart disease1−9 have been elucidated by right heart catheterization. Relatively little information, however, regarding the acute hemodynamic effects of ouabain or digoxin on right atrial pressure and on cardiac output (measured by the Fick technic with right atrial sampling) in three patients with aortic stenosis. A decline in mean right atrial pressure occurred in these patients and a small elevation of cardiac out-

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**Table 2**

*Acute Hemodynamic Effects of Ouabain in Valvular Aortic Stenosis*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Condition</th>
<th>L.A. press. (mean)</th>
<th>L.V. press. s/d</th>
<th>B.A. press. s/d</th>
<th>Peak gradient (L.V.-B.A.) L./Min./M.²</th>
<th>Cardiac index</th>
<th>Vent. rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.D.</td>
<td>Control</td>
<td>19</td>
<td>214/24</td>
<td>113/54</td>
<td>101</td>
<td>2.42</td>
<td>72</td>
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<tr>
<td></td>
<td>50 min. post</td>
<td>0.6 mg. ouabain</td>
<td>15</td>
<td>246/22</td>
<td>110/53</td>
<td>130</td>
<td>3.62</td>
</tr>
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<td>R.R.</td>
<td>Control</td>
<td>14</td>
<td>186/24</td>
<td>110/41</td>
<td>76</td>
<td>2.70</td>
<td>66</td>
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<tr>
<td></td>
<td>50 min. post</td>
<td>0.6 mg. ouabain</td>
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<td>210/24</td>
<td>130/41</td>
<td>80</td>
<td>4.12</td>
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<td>R.K.</td>
<td>Control</td>
<td>9</td>
<td>264/23</td>
<td>104/60</td>
<td>160</td>
<td>3.50*</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>50 min. post</td>
<td>0.75 mg. ouabain</td>
<td>6</td>
<td>289/21</td>
<td>118/62</td>
<td>171</td>
<td>2.82</td>
</tr>
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<td>C.B.</td>
<td>Control</td>
<td>11</td>
<td>219/21</td>
<td>129/72</td>
<td>90</td>
<td>2.36*</td>
<td>70</td>
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<tr>
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<td>11</td>
<td>234/16</td>
<td>133/69</td>
<td>101</td>
<td>2.54</td>
</tr>
<tr>
<td>J.O.</td>
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<td>107/66</td>
<td>74</td>
<td>N.M.</td>
<td>75</td>
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<tr>
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<td>40 min. post</td>
<td>0.75 mg. ouabain</td>
<td>N.M.</td>
<td>214/13</td>
<td>124/66</td>
<td>90</td>
<td>N.M.</td>
</tr>
<tr>
<td>C.S.</td>
<td>Control</td>
<td>14</td>
<td>190/25</td>
<td>125/65</td>
<td>65</td>
<td>N.M.</td>
<td>100</td>
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<tr>
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<td>0.75 mg. ouabain</td>
<td>12</td>
<td>204/22</td>
<td>128/67</td>
<td>76</td>
<td>N.M.</td>
</tr>
</tbody>
</table>

**SYMBOLS:** L.A., left atrial pressure; L.V., left ventricle; B.A., brachial artery; s/d, systolic/end-diastolic; Vent., ventricular; N.M., not measured.

All pressures and gradients expressed in mm. Hg.

*Indicates values not obtained in duplicate.
put, of questionable significance, was noted in two of them. Yu and collaborators observed that acetylstrophanthidin produced a small elevation of the cardiac output and a decline in the pulmonary capillary wedge pressure in one patient with aortic stenosis.18

It has been pointed out elsewhere that large differences between the mean left atrial pressure and the left ventricular end-diastolic pressure may exist in patients with left ventricular hypertrophy.10 For this reason estimates of left ventricular end-diastolic pressure from pulmonary capillary wedge pressure or even from mean left atrial pressures are not warranted; in order to assess the effects of any intervention on left ventricular function it is necessary to measure the left ventricular pressure directly. Of the various technics of left heart catheterization that have been developed, only retrograde aortic catheterization and transseptal left heart catheterization are suitable for providing measurements of left heart pressures with the patient in a basal and steady state over time periods long enough to evaluate the effects of a cardiac glycoside. Retrograde aortic catheterization may be difficult or impossible in patients with obstruction to left ventricular outflow and, by the presence of the catheter in the narrowed aortic orifice, this technic has the additional disadvantage of further reducing the already markedly attenuated orifice size. For these reasons transseptal left heart catheterization was employed in these studies.

In the patients with valvular aortic stenosis, ouabain either improved left ventricular function or had no discernible effect on it, but in no patients did this drug have a deleterious effect. The left ventricular end-diastolic pressure generally fell slightly or re-

Figure 1
Acute hemodynamic effects of ouabain in patient J.D. with valvular aortic stenosis. LV, left ventricular systolic pressure; LVED, left ventricular end-diastolic pressure; BA, brachial artery systolic pressure; BAd, brachial artery diastolic pressure.

Figure 2
Acute hemodynamic effects of ouabain in patient C.B. with valvular aortic stenosis. Symbols same as in figure 1.

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mained unchanged, while the cardiac output rose strikingly in two patients and showed little change in the other two in whom it was measured; the elevation of the systolic pressure gradient is considered to have resulted from the increase in the stroke volume that occurred in all but one patient in whom it was measured. The slight increases in the “effective” orifice size calculated by the Gorlin formula may have resulted from minimal enlargement of the aortic orifice as a result of the increase in left ventricular and arterial pressures (figs. 1 and 2). Failure of the left ventricular end-diastolic pressure to fall dramatically is in sharp contrast to the decline in right ventricular end-diastolic pressure that cardiac glycosides produce in patients with cor pulmonale and right ventricular failure secondary to pulmonary hypertension. A possible explanation for this finding is that the elevation of the left ventricular end-diastolic pressure is related primarily to the altered ventricular distensibility resulting from the concentric myocardial hypertrophy that occurs in this condition and is not due to left ventricular dilatation and failure. Accordingly, even though digitalis glycosides may be capable of augmenting myocardial contractility, these drugs do not result in a marked reduction of elevated ventricular end-diastolic pressure.

In contrast to the findings in the patients with valvular aortic stenosis, ouabain consistently produced an elevation of left ventricular end-diastolic pressure and of left atrial pressure in the patients with hypertrophic subaortic stenosis; the cardiac output either fell or remained unchanged, and the systolic pressure gradient between the left ventricle and the brachial artery rose in all four patients.
Among the various anatomic types of obstruction to left ventricular ejection, hypertrophic subaortic stenosis is unique in that in this condition the resistance to blood flow is created by muscular narrowing of the outflow tract during ventricular systole. Whereas the narrowed orifice that occurs in the discrete forms of aortic valvular, subvalvular, or supravalvular stenosis remains relatively fixed in size throughout the cardiac cycle, the obstruction associated with hypertrophic subaortic stenosis increases as systole progresses and subsides during diastole. This characteristic of hypertrophic subaortic stenosis is responsible for many of the clinical and hemodynamic features characteristic of this disease.

In a previous communication data were presented indicating that in these patients

### Table 3

<table>
<thead>
<tr>
<th>Patient</th>
<th>Condition</th>
<th>L.A. press. (mean)</th>
<th>L.V. press. s/d</th>
<th>B.A. press. s/d</th>
<th>Peak gradient (L.V.-B.A.)</th>
<th>Cardiac index L./Min./M.²</th>
<th>Vent. rate</th>
</tr>
</thead>
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<td>84</td>
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<td>180/45</td>
<td>105/64</td>
<td>75</td>
<td>2.22</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>50 min. post</td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td></td>
<td>0.75 mg. ouabain</td>
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<td>B.G.</td>
<td>Control</td>
<td>8</td>
<td>117/11</td>
<td>97/52</td>
<td>20</td>
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<td></td>
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<tr>
<td>M.W.</td>
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<td>13</td>
<td>158/29</td>
<td>100/61</td>
<td>58</td>
<td>2.65</td>
<td>84</td>
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<td>60 min. post</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.50 mg. ouabain</td>
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SYMBOLS: L.A., left atrial pressure; L.V., left ventricle; B.A., brachial artery; s/d, systolic/end-diastolic; Vent., ventricular.

All pressures and gradients expressed in mm. Hg.
the degree of obstruction is a function of the force of ventricular contraction. While the more forceful contraction following the compensatory pause coming after a premature ventricular contraction was consistently associated with a reduction in stroke volume, it was only possible to speculate on the effects of a sustained increase in contractile force. It was postulated, however, that inotropic drugs may exert a deleterious effect by increasing the severity of the obstruction and the work load on the left ventricle, without improving the cardiac output. The observations on the effects of ouabain presented above are consistent with this postulate. Digitalis glycosides are known to increase the force of myocardial contraction and the rate of pressure development in compensated as well as in failing hearts, and it seems likely that the muscular outflow tract of patients with hypertrophic subaortic stenosis participates in this inotropic response. It therefore appears that ouabain intensified the systolic obstruction, and thereby elevated ventricular end-diastolic pressure in spite of its positive inotropic effect. Accordingly, digitalis glycosides should be administered with considerable caution to patients with idiopathic hypertrophic subaortic stenosis.

Summary

The acute hemodynamic effects of 0.50 to 0.75 mg. ouabain were studied in six patients with valvular aortic stenosis and in four patients with idiopathic hypertrophic subaortic stenosis. Left atrial and left ventricular pressures were determined by means of transseptal left heart catheterization and cardiac output was measured by the indicator-dilution technic. In the patients with valvular aortic stenosis, ouabain either improved left ventricular function or had no discernible effect on it, but in no patient was left ventricular function depressed. Left ventricular end-diastolic pressure fell slightly or remained unchanged, while cardiac output rose in two of four patients. In the patients with hypertrophic subaortic stenosis, the left ventricular end-diastolic pressure and mean left atrial pressure rose significantly following ouabain administration; cardiac output either fell or remained unchanged and the systolic pressure gradient between the left ventricle and the brachial artery rose. These actions of ouabain in hypertrophic subaortic stenosis are considered to result from a sustained increase in left ventricular contractile force that increased the obstruction produced by the muscular outflow tract.

References

9. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., and Alexander, J. K.: Some effects of digoxin...


Men who experiment, despite all their dexterity, cannot solve problems unless they are inspired by a fortunate hypothesis based on accurate and well-made observations. Finally men who generalize can make lasting theories only in so far as they themselves learn all the scientific details that these theories are intended to represent. Scientific generalization must proceed from particular facts to principles; and principles are the more stable as they rest on deeper details, just as a stake is the firmer, the farther it is driven into the ground.—Claude Bernard. An Introduction to the Study of Experimental Medicine. New York, The Macmillan Company, 1927, p. 26.
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