Studies on Digitalis

XV. Effects of Cardiac Glycosides on Myocardial Force-Velocity Relations in the Nonfailing Human Heart

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WHILE there is general agreement that digitalis glycosides improve the contractile properties of failing myocardium, the actions of these drugs on the nonfailing heart are less clear. In the absence of heart failure, acute digitalization either depresses or produces no significant change in the cardiac output,1-6 and such observations have led to the suggestion that digitalis does not exert a positive inotropic effect in the nonfailing heart.2, 5, 7, 8 On the other hand, in open-chest studies on anesthetized dogs presumed to have normal hearts, cardiac glycosides have been shown to increase the contractile force of both the ventricles9 and the atria10 and to elevate the ventricular function curve.9 These observations have been extended to patients without heart failure in whom following the administration of cardiac glycosides an increase in ventricular contractile force has been observed at the time of corrective cardiac operations.11 It was appreciated that the interpretation of the latter finding was necessarily limited, since the hearts were not normal and since the general anesthetia or the surgical procedure itself could have depressed myocardial function. Further support for the view that digitalis glycosides do increase the contractile state of the normal human heart was provided by the observation that the rate of intraventricular pressure development is augmented by ouabain in conscious human subjects without heart disease.12

Daggett and Weisfeldt13 have recently re-examined the effects of acetylstrophanthidin on the myocardial contractility of the nonfailing dog heart. These workers observed that acetylstrophanthidin did not elevate the ventricular function curve in intact animals and concluded that since this drug “increased contractility only in dogs deprived of autonomic control of cardiac performance, reflex factors play an important role in the acutely observed results of glycoside administration in the intact animal.”

The possibility has been considered that the discrepancies in these conclusions concerning the action of digitalis might be based on the specific technique employed for measuring the contractile properties of the heart. In the past few years, it has become increasingly apparent that the concepts derived and utilized by Hill14 and his collaborators in the analysis of the physiological behavior of skeletal muscle can also be applied to heart muscle.15-18 Basically, an inverse relation has been shown between the force of contraction, that is, the load the muscle carries, and its velocity of shortening, and it now appears that the position of the force-velocity curve which describes this relation serves as the most precise measure of the contractile state of the myocardium.

It has been shown that the force-velocity curve of isolated papillary muscles removed from patients with heart failure are shifted upward and to the right by the addition of strophanthidin.19 More recently, an investigation of the relation between the action of digitalis and cardiac norepinephrine stores demonstrated that glycosides also shift the force-velocity curves of papillary muscles obtained from normal cats as well as from

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animals which had previously undergone chronic cardiac denervation. The major purpose of the present investigation was to study the effects of therapeutic doses of a digitalis glycoside on the contractile properties of the intact, nonfailing human heart by measuring the effects of ouabain on myocardial force-velocity relations.

Methods

Myocardial force-velocity relations were studied in six subjects, five women and one man, who ranged in age from 20 to 36 years. All had undergone corrective cardiac operations 6 months to 1 year prior to the study. Four had closure of atrial septal defects, one had closure of a ventricular septal defect, and one had a closed valvulotomy for mitral stenosis. The effects of ouabain administration were determined at postoperative cardiac catheterization. At the time of study the patients were asymptomatic and had normal cardiac indices. Five patients had normal pulmonary artery and right ventricular pressures. Patient B.B. had residual pulmonary hypertension, but in her the effects of ouabain on left rather than on right ventricular force-velocity relations were studied.

Each of the six patients received 0.01 mg/kg of ouabain intravenously and recordings were made prior to the drug and 30 minutes later. Cardiac output was measured at these times by means of the indocyanine-green dye-dilution method. The mean left ventricular systolic ejection rate (MSER) in cc/m²/sec was calculated by dividing stroke volume in cc/m² of body surface area by the duration of ejection in seconds, as determined from the arterial pressure tracing.

The techniques employed have been described in detail previously. At the time of corrective cardiac operation small silver-tantalum markers had been sutured to the surface of the right or left ventricle. In order to obtain the data necessary to evaluate the force-velocity relation, cineradiograms were exposed at 30 frames per second, while intraventricular pressure pulses were recorded simultaneously on an oscilloscopic photographic recorder at a paper speed of 100 mm/sec. Intraventricular pressures were recorded through cardiac catheters by means of Statham P23D pressure transducers or with an Allard-Laurens catheter tip manometer. A mechanical marker was activated by the R wave of the electrocardiogram, and the recording of its motion on the cineradiogram as well as on the pressure tracing allowed precise correlation of ventricular dimensions and pressures. Subsequently, the distances between the markers on the ventricle were measured on successive cineradiographic frames. Only markers which had been placed in a manner so that they were parallel to the frontal plane were used, to minimize rotational errors. All observations were made with the patient in the supine position, and to eliminate the effect of respiration on ventricular dimensions, all measurements were made in expiration. The distance between markers could be measured reproducibly to within 0.5 mm.

From studies on the force-velocity relationships in the isolated cat papillary muscle, it is clear that throughout active contraction, the force-velocity curve, at any instant, is determined by both the instantaneous length of the muscle and by its contractile state. Thus, if the force-velocity relation is always examined at the same muscle length, the contractile state of the myocardium will be delineated uniquely for that particular instantaneous muscle length. Accordingly, the velocity of a segment of the patient's ventricular myocardium was determined when the segment of myocardium passed through the same length, both in the control state and following ouabain. This length was termed the "isorelength." Further, although intramyocardial tension could not be measured directly, it is known from Laplace's law that at any particular ventricular volume wall tension is a constant function of ventricular pressure. Therefore, in order to use intraventricular pressure as a direct reflection of wall tension, ventricular pressures were always measured at the instant at which ventricular dimensions passed through the isorelength point, at which the velocity of marker shortening was also measured. It is now clear that at any given muscle length an increase in velocity at a constant tension (force), an increase in tension at a constant velocity, or increases of both tension and velocity indicate an augmentation of the contractile state of the heart.

Results

Following the administration of ouabain, heart rate remained essentially constant in two patients (J.O.R. and J.V.) and decreased by between 10 and 34 beats per minute in the others. The ventricular end-diastolic dimensions (table 1, VEDL) were reduced slightly in all but one patient (figs. 1 and 2), and in that exception (G.C.), a considerable reduction in heart rate and a substantial increase in stroke index occurred. The contractile state of the myocardium was augmented in all instances, as evidenced by a shift of the force-velocity relations upward and to the right. Velocity at the isorelength point increased.
Summary of Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>B.S.A. (m²)</th>
<th>RV s/d (mm Hg)</th>
<th>PA s/d (mm Hg)</th>
<th>BA s/d (mm Hg)</th>
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<td>S.H.</td>
<td>P.O.ASD</td>
<td>34</td>
<td>F</td>
<td>1.78</td>
<td>22/2</td>
<td>15</td>
<td>129/79</td>
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<td>M.H.</td>
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<td>36</td>
<td>F</td>
<td>1.60</td>
<td>16/3</td>
<td>12</td>
<td>102/60</td>
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<td>J.O'R.</td>
<td>P.O.ASD</td>
<td>37</td>
<td>M</td>
<td>1.90</td>
<td>27/8</td>
<td>14</td>
<td>130/60</td>
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<tr>
<td>G.C.</td>
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<td>15/0</td>
<td>10</td>
<td>125/72</td>
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<td>B.B.†</td>
<td>P.O.M.S.</td>
<td>33</td>
<td>F</td>
<td>1.83</td>
<td>59/5</td>
<td>45</td>
<td>122/66</td>
</tr>
<tr>
<td>J.V.</td>
<td>P.O.VSD</td>
<td>20</td>
<td>F</td>
<td>1.42</td>
<td>14/2</td>
<td>7</td>
<td>102/54</td>
</tr>
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Abbreviations: P.O., postoperative; ASD, atrial septal defect; VSD, ventricular septal defect; MS, mitral stenosis; B.S.A., body surface area; RA, mean right atrial pressure; s/d, systolic pressure/diastolic pressure; m, mean pressure; PA, mean pulmonary artery pressure; BA, mean brachial artery pressure; VEDL, ventricular end-diastolic segment length; ISL, isoenlength point; PressureISL, intraventricular pressure at the isoenlength point; VelocityISL, velocity of shortening at isoenlength point; MSER, left ventricular mean systolic ejection rate.

*Each value represents the average of 10 measurements.
†Measurements of left ventricular end-diastolic segment length (VEDL), pressureISL, and velocityISL. All other measurements are from the right ventricle.

by an average of 77 ± 5 (SEM)%, while intraventricular pressure at the same isoenlength rose an average of 23 ± 6%. Examples of shifts in the force-velocity relation are shown in figures 3 and 4 for the right and left ventricles, respectively. Despite this clear augmentation of the

**Figure 1**

The effects of ouabain on the dimensions and the course of right ventricular contraction. The distance between opaque markers on the surface of the right ventricle are shown for patient M.H. The horizontal dashed line represents the isoenlength point at which velocity of marker movement (the oblique dashed line) was measured.

**Figure 2**

The effects of ouabain on the end-diastolic dimensions and the course of left ventricular contraction for subject B.B. Measurements are similar to those in figure 1. Below are shown the corresponding values for cardiac index (C.I.), stroke index (S.I.), left ventricular ejection time (E.T.) and the mean systolic ejection rate (MSER).
STUDIES ON DIGITALIS

<table>
<thead>
<tr>
<th>Heart rate/min</th>
<th>VEDL</th>
<th>Pressure*ISL</th>
<th>Velocity*ISL</th>
<th>% Change in velocity from control</th>
<th>Cardiac index (L/min/m²)</th>
<th>Stroke index (cc/beat/m²)</th>
<th>Ejection time (msec)</th>
<th>MSER (cc/sec/m²)</th>
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</table>

**Figure 3**

The effects of ouabain on the instantaneous force-velocity relations of the ventricle from the same patient study as illustrated in figure 1. On the ordinate is the velocity of shortening of the segment of myocardium between the markers at the isovelocity point and on the abscissa is the corresponding right ventricular pressure. Each point represents a single ventricular contraction and the crossbars represent one standard deviation.

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**Figure 4**

The effects of ouabain on the force-velocity relations of the left ventricle on the same patient and study as in figure 2. Legend as described in figure 3. The contractile state of the myocardium as indicated by the shifts in the instantaneous force-velocity relations, the cardiac index either fell slightly (S.H.) or remained esse-
tially unchanged. The left ventricular ejection time showed no consistent change, rising slightly in one patient (G.C.) in whom heart rate fell markedly and falling in the other three in whom it was measured. The mean left ventricular systolic ejection rate rose in all four patients in whom it was measured, but only by an average of 7%.

Discussion

In order to place the results of this investigation on the effects of a cardiac glycoside on the force-velocity relation of the intact human heart into proper perspective, it is helpful first to consider the effects of digitalis on the isolated papillary muscle of the cat as studied by techniques described in detail elsewhere.\textsuperscript{17} Figure 5 (A) illustrates the effects of the glycoside on the course of isometric tension when the papillary muscle was not allowed to shorten and the initial length was held constant. It is apparent that in addition to a marked increase in peak tension, the time interval between stimulation and peak tension was reduced; therefore, the rate of tension development was greatly augmented by the glycoside, suggesting that the velocity of shortening of the contractile elements had increased. A more direct measurement of the effects of strophanthidin on contractile element velocity is shown in figure 5 (B), representative of studies on seven muscles obtained from normal cats.\textsuperscript{20} Each point on this panel was obtained from a separate contraction. The initial length of the muscle was set by a small preload which was maintained constant for both curves. The effect on the initial velocity of isometric shortening of progressively increasing the load faced by the muscle during systole, that is, the afterload, was then determined. The addition of strophanthidin to the bath shifted the force-velocity relation of the cat papillary muscle upward and to the right, increasing the maximum velocity of shortening, that is, the velocity of shortening without an afterload by an average of $80 \pm 8\%$ while augmenting maximum isometric force by an average of $57 \pm 7\%$.\textsuperscript{20}

The findings in the intact human heart are analogous to those observed in the cat papillary muscle. Although the technique utilized in man does not permit elucidation of the entire force-velocity curve, it does allow definition of comparable points on the force-velocity curves before and after the glycoside.

![Figure 5](http://circ.ahajournals.org/)

\textit{Figure 5}

\textit{The effects of the digitalis glycoside strophanthidin on the course of isometric contraction (A) and the force-velocity relation (B) of the cat papillary muscle.}

\textit{Circulation, Volume XXXIV, September 1966}
With measurements carried out at the same ventricular dimensions before and after ouabain, both myocardial force (tension) and velocity of shortening increased in every patient studied, signifying a shift of the force-velocity curve upward and to the right. It is likely that this augmentation of the velocity of shortening reflects an increase in the rate of interactions at the myofibrillar contractile sites. It is of interest that ouabain produced these large shifts of the force-velocity relation despite the fact that cardiac output did not rise and ventricular dimensions were not greatly altered. Indeed, in one patient (table 1, S.H.), cardiac output fell significantly while velocity of shortening more than doubled. These findings are in accord with the concept that the cardiac output is controlled by numerous factors, of which the contractility of the myocardium is only one. In the absence of heart failure, the augmentation of myocardial contractility produced by glycosides may not be accompanied by an increase in cardiac output, since under these circumstances contractility does not limit the cardiac output. In contrast, however, in the presence of heart failure, the reduced contractility is primarily responsible for depression of the cardiac output, and augmentation of contractility produced by cardiac glycosides does elevate the output. Thus, it is becoming increasingly clear that determination of the effects of a drug on cardiac output does not necessarily provide an assessment of its actions on the contractile state of the myocardium. Therefore, the finding that glycosides fail to increase the cardiac output in normal subjects in no way excludes a positive inotropic action.

As already noted, Daggett and Weisfeldt have concluded that glycosides produced no net effect on myocardial contractility in reflexly intact animals since the relation between left ventricular end-diastolic pressure and stroke work remained unaltered after the drug had been administered. However, these workers noted a marked increase in the rate of rise of intraventricular pressure at constant ventricular end-diastolic pressure and cardiac output, despite the fact that the ventricular function curve was unaltered. It appears likely that this increase in the rate of ventricular pressure reflected a displacement of the force-velocity relation, but that this augmentation of contractility was not reflected in the ventricular function curve. This view is further supported by other work from this laboratory in which a comparison of force-velocity relations and ventricular-function curves in the intact canine heart clearly demonstrated the greater sensitivity and added information concerning the speed of myocardial shortening contained in the force-velocity relation.

A final point of interest in this investigation concerns the relatively minor increases in the left ventricular mean systolic ejection rates (average = 7%) occurring in the face of such marked increments in the velocity of myocardial shortening (average = 77%). A previous study has also directed attention to this discrepancy and when the results of both investigations are considered together they may be interpreted as showing that the mean systolic ejection rate does not accurately reflect the velocity of myocardial fiber shortening.

Summary

The effects of ouabain (0.01 mg/kg) on ventricular force-velocity relations were studied in six patients who had previously undergone corrective cardiac operations. The technique employed consisted of exposing cineradiograms at 30 frames per second and measuring the velocity of movement of roentgen-opaque markers that had been sutured to the external surfaces of the ventricles while simultaneously recording intraventricular pressures. A beat-to-beat analysis of the ventricular force-velocity relation was then accomplished by relating the velocity of marker movement and intraventricular pressure at constant ventricular dimensions. It was observed that ouabain always augmented myocardial contractility as reflected in the force-velocity relation. Velocity of shortening increased an average of 77 ± 5 (SEM)% while intraventricular pressure rose by an average of 23 ± 6%. Despite this improvement in contractility, no consistent
changes in cardiac output were observed. Analogous changes in force-velocity curves were obtained when a cardiac glycoside was added to isolated papillary muscles removed from normal cats. It is concluded that the fundamental action of digitalis glycosides is to augment the contractile state of the heart, whether normal or failing, but that in the absence of heart failure this improvement is not translated into an increase in cardiac output.

References


On Scientific Pursuits and Discoveries

Of the many traits recognized among scientists, the most essential—indeed, almost a sine qua non—is some form of intellectual curiosity. H. L. Mencken believed that the prototype of the scientist “is not the liberator releasing slaves, the good samaritan lifting up the fallen, but a dog sniffing tremendously at an infinite series of rat holes.” This curiosity leads to questions that each individual tries to answer according to his own temperament. There is, in truth, no such thing as a method of discovery. The solution of a problem may come to one man after immense systematic analysis, to another by analogy, to a third as a sudden thought or vision, to yet another as a dream, or in many other ways. There is a method for scientific verification or demonstration, but that is a different thing from discovery.—René Dubos: The Dreams of Reason: Science and Utopias. New York, Columbia University Press, 1961, p. 136.
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