Effects of Chronic Heart Failure on the Inotropic Response of the Right Ventricle of the Conscious Dog to a Cardiac Glycoside and to Tachycardia

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SUMMARY
The effects of ouabain, 20 μg/kg, and elevation of cardiac rate from 90 to 240 beats/min (Bowditch phenomenon) were examined on right ventricular (RV) segment length (SL), pressure (P), velocity of shortening (V), dP/dt, and dP/dt/P in conscious dogs before and after chronic right heart failure was induced by tricuspid avulsion and pulmonary stenosis, or by pulmonary stenosis alone. Chronic pulmonary stenosis and tricuspid regurgitation increased RV systolic P from 25 ± 3 to 59 ± 7 mm Hg, end-diastolic P from 3 ± 1 to 16 ± 2 mm Hg and reduced dP/dt/P from 48 ± 6 to 24 ± 4 sec⁻¹ and V from 26 ± 3 to 15 ± 3 mm/sec. Both ouabain and tachycardia exerted relatively minor inotropic effects in normal, healthy, conscious dogs; dP/dt/P and V rose by 18 ± 2 and 17 ± 2% with ouabain, and by 15 ± 3 and 16 ± 3% with tachycardia. When the tachycardia-induced reductions in end-diastolic SL were prevented by saline infusion, the increases in dP/dt/P and V were 19 ± 3% and 21 ± 3%. After chronic heart failure had been induced, the positive inotropic increases, with ouabain and tachycardia expressed on an absolute or relative basis, were significantly greater than had occurred in the dogs prior to heart failure; dP/dt/P and V rose by 47 ± 5 and 48 ± 6% with ouabain and by 41 ± 4% and 51 ± 3% with tachycardia. Thus, cardiac glycosides and the Bowditch phenomenon exert relatively minor positive inotropic responses in the nonfailing heart of the conscious dog when compared with the responses to these stimuli in the failing heart.

Additional Indexing Words:
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Studies Conducted in Strips of Isolated Cardiac Muscle or in Hearts Depressed by General Anesthesia Attribute a Positive Inotropic Action Both to Cardiac Glycosides¹-⁷ and to the Bowditch Phenomenon, i.e., the Elevation of Cardiac Frequency.⁸-¹⁸ It has been demonstrated in our laboratory that the augmentation of contractility induced by these two interventions is less in the normal hearts of conscious animals than in the normal hearts acutely depressed by general anesthesia or by large doses of propranolol.¹⁹,²⁰ However, it is not clear whether myocardial depression-induced by chronic cardiac failure similarly modifies the inotropic response to cardiac glycosides and tachycardia. In order to compare the effects of these interventions on the normal and failing myocardium of conscious animals, right ventricular pressure and dimensions, dP/dt, and velocity of myocardial fiber shortening were measured directly in conscious dogs when the animals were normal, and the measurements were repeated as heart failure was induced by the combination of progressive pulmonary constriction and tricuspid avulsion or by pulmonary constriction alone.

Methods
Nine mongrel dogs, weighing between 25 and 35 kg, were anesthetized with sodium pentobarbital, 30 mg/kg. Through a thoracotomy in the fourth right intercostal space, miniature pressure gauges were implanted within the right ventricle through a stab wound in the apex. Opposing miniature ultrasonic diameter transducers were implanted at Konigsberg P22, Konigsberg Instruments, Pasadena, California. Construction details available from author.
by examination of the received signal on the oscilloscope and confirmed at autopsy.

Experiments were conducted 2–4 weeks after operation. While the conscious, unsedated dogs rested quietly, control records of right ventricular SL and pressure (P), rate of change of SL (dSL/dt), i.e., the velocity of myocardial shortening (V), the rate of change of pressure, dP/dt and heart rate were obtained. These variables were continuously recorded during all interventions. Cardiac rate was increased in steps of 30 beats/min using an electronic stimulator, starting from a rate slightly above the spontaneous rate; each level was maintained for 30 sec. This experimental sequence was repeated three times in each dog prior to and after the development of heart failure. On one occasion in each dog RV end-diastolic SL was maintained constant while heart rate was elevated by continuously infusing saline intravenously. Maximal inotropic response to pacing occurred at different frequencies in different dogs. Accordingly, the peak responses were chosen to control rather than responses at any given cardiac frequency.

On a separate day, after control recordings were taken in spontaneous rhythm and with heart rate paced at a frequency slightly above the spontaneous rate, ouabain, 20 ug/kg, was administered as a bolus i.v. Measurements were recorded continuously until the peak inotropic effects of the drug were noted; this occurred within 30 minutes in the normal dogs and 2 hours in the presence of heart failure. During this interval, heart rate was elevated to the control paced rate every 5 min and maintained for one minute. The effects of increasing heart rate and ouabain were restudied separately in these dogs after right heart failure had been induced by the technique described above.

Data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph at a paper speed of 100 mm/sec. A cardiotachometer, triggered by the signal from the pressure pulse, provided instantaneous and continuous records of heart rate. Continuous records of dP/dt and dSL/dt were derived from the right ventricular pressure and SL signals, using Philbrick operational amplifiers connected as differentiators having frequency responses of 60 and 30 Hz respectively. A triangular wave signal with known slope (rate-of-change) was substituted for pressure and SL signals to calibrate directly the dP/dt and dSL/dt channels.

The effects of interventions on myocardial force-velocity relations were assessed by determining their effects on the velocity (V) of shortening and intraventricular pressure (P) at an identical ventricular SL (isotension point), i.e., Viso, by the technique described in detail previously for left ventricular measurements. Isotension points were obtained during the first one-third of ejection, except in the experiments involving pacing when end-diastolic size fell substantially; in these experiments peak velocity (V) measurements were used. In addition, the effects on peak dP/dt and the quotient of dP/dt and developed pressure (right ventricular isovolumic minus end-diastolic pressure), i.e., dP/dt, were examined. The same level of pressure which occurred during isometric contraction, before and after each intervention, was used for this calculation and dP/dt was determined at that level of pressure. This technique for evaluating the myocardial contractile state for the left ventricle has also been described in detail previously.

**Figure 1**

Schematic diagram of implanted ultrasonic crystals and pressure gauge in the right ventricle and typical waveforms of right ventricular (RV) segment length (SL), velocity, and pressure.  

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*Medtronic, Inc., Minneapolis, Minn.

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In order to determine the sensitivity of this method of evaluating the myocardial contractile state of the right ventricle, in another series of experiments, in six normal conscious dogs, isoproterenol, 0.4 to 0.8 μg/kg, was administered as a bolus i.v. to reduce RV end-diastolic SL by a similar amount as occurred with elevating heart rate. Isoproterenol exerted a potent inotropic action in the normal right ventricle; dP/dt/P rose from 50 ± 5 to 242 ± 17 sec⁻¹ and end-systolic SL fell more than end-diastolic SL, indicating that an increase in the extent of myocardial fiber shortening per stroke had occurred. Norepinephrine also induced large increases in RV velocity, dP/dt and dP/dt/P, while myocardial depressant doses of propanolol and pentobarbital anesthesia induced the expected reductions in RV velocity, dP/dt, and dP/dt/P. Changes in the end-diastolic and end-systolic measurements of segment length correlated well with our experience from studies using other techniques to measure ventricular dimensions, e.g., left ventricular diameter measurements in conscious dogs and cineangiographic techniques for volume measurements in man. Specifically, RV end-diastolic segment length rose with increases in afterload (abrupt inflation of the pulmonary occluder) and preload (saline infusion) and fell with decreases in afterload (release of pulmonary occlusion) and preload (hemorrhage). These techniques were evaluated in the dogs both before and after induction of heart failure. It was considered that tricuspid insufficiency would interfere with the usefulness of the dP/dt/P measurement as an indicator of myocardial contractility. However, other studies have indicated that this measurement is useful in the assessment of left ventricular contractility in the presence of mitral insufficiency. Moreover, the responses to catecholamines as well as pacing and ouabain in the dogs with heart failure due to pulmonary stenosis alone were not significantly different from those in the animals with tricuspid insufficiency and pulmonary stenosis. Average and SEM values were calculated. Control and response values were compared in the same animals using a paired t-test. Changes from control with interventions were compared using the paired t-test.

Results

Effects of Heart Failure

Combined pulmonary stenosis and tricuspid insufficiency increased systolic RV pressure from 25 ± 3 to 59 ± 7 mm Hg, RV end-diastolic pressure from 3 ± 1 to 16 ± 2 mm Hg, and heart rate from 74 ± 5 to 114 ± 7 beats/min and decreased dP/dt/P from 48 ± 6 to 24 ± 4 sec⁻¹ and peak V from 26 ± 3 to 15 ± 3 mm/sec (fig. 2). RV end-diastolic SL rose from 11.3 to 14.5 mm, while end-systolic SL increased from 8.4 to 12.7 mm. All of these changes were significant (P < 0.01). In the three animals with pulmonary stenosis RV pressure (systolic/end-diastolic) rose from an average control of 27/3 to 86/13 mm Hg. Heart rate increased from 78 to 120 beats/min, while peak velocity fell from 25 to 11 mm/sec and dP/dt/P from 52 to 28 sec⁻¹. The responses to ouabain and pacing were not significantly different in the dogs with pulmonary stenosis alone or in those with combined lesions.

Figure 3

Maximal effects of ouabain on right ventricular performance in a normal, conscious dog; recordings of phasic right ventricular (RV) segment length (SL) (top panel); velocity of segment length shortening (V) (second panel); systolic and diastolic pressures (P) (third and fourth panels); dP/dt (fifth panel); and heart rate (HR) (bottom panel). DIG = after ouabain.
Digitalis and Pacing in Heart Failure

Effects of Ouabain

Normal Heart. Ouabain, 20 μg/kg, caused a positive inotropic response within one minute of administration; this reached a peak between 15 and 45 minutes (average = 30 min) and then began to subside gradually. By 1 to 2 hours all values had returned to pre-ouabain control levels. During the peak inotropic response ouabain increased systolic RVP from 28 ± 2 to 40 ± 3 mm Hg, but did not affect RV end-diastolic P or SL significantly, while RV end-systolic SL decreased by 0.2 ± 0.06 mm (P < 0.05). RV dP/dt/P rose by a maximum of 18 ± 2% from a control of 48 ± 6 sec⁻¹ while V rose by 17 ± 2% from a control of 26 ± 3 mm/sec (P < 0.01) (fig. 3). Heart rate, which had fallen initially after ouabain, was not significantly different from the control level at the time of the peak inotropic response. Also, when measurements were made at a constant heart rate, the changes in contractility produced by ouabain were not significantly different from those observed in spontaneous rhythm.

Failing Heart. In the heart failure state ouabain exerted a more potent positive inotropic response (fig. 4); dP/dt/P rose by 47 ± 5% from a control of 24 ± 4 sec⁻¹ and V by 48 ± 6% from a control of 15 ± 3 mm/sec (fig. 5). The increases in dP/dt/P and V were greater (P < 0.01) on an absolute as well as a percentage basis in the failing compared to the normal heart.

Systolic RVP rose by 16 ± 2 mm Hg, RV end-diastolic P fell by 4 ± 1 mm Hg, RV end-systolic SL fell more (−0.73 ± 0.07 mm) than end-diastolic SL, (−0.21 ± 0.04 mm) (P < 0.01). Thus, the extent of myocardial fiber shortening per stroke rose. Not only was the magnitude of the positive inotropic response greater in the presence than in the absence of heart failure, but the duration was greater as well in all dogs studied (fig. 6); two hours after administration of ouabain, dP/dt/P and velocity had fallen only slightly.

Effects of Tachycardia

Normal Heart. Increasing cardiac frequency in steps from 90 to 240 beats/min did not affect RV pressure significantly, while RV end-diastolic and end-systolic SL fell progressively and by maximum amounts of 0.84 ± 0.05 and 0.33 ± 0.05 mm, respectively. RV dP/dt/P rose by a maximum of 15 ± 3% from a control of 48 ± 6 sec⁻¹ and peak V by 16 ± 3% from a control of 26 ± 3 mm/sec. When RV end-diastolic size was prevented from falling during pacing by the infusion of saline, the increases in dP/dt/P

Figure 4
Maximal effects of ouabain on right ventricular performance in the heart failure state. See figure 3 legend for identification of panels.

Figure 5
Comparison of the average (± SEM) increases in dP/dt/P and velocity with ouabain (top) and tachycardia (bottom) before and after heart failure had been induced. Control values are shown at the bottom of the bars.
Comparison of the effects of ouabain in the same animal before (triangles) and after (circles) heart failure had been induced. Not only was the peak effect greater but the positive inotropic action of the drug was more sustained in the failing heart. Baseline measurements are shown at the left.

(+19 ± 3%) and $V_{\text{ANO}}$ (+21 ± 3%) from similar control values prior to pacing without infusion were slightly greater ($P < 0.05$), but still relatively minor in comparison with the responses in heart failure. In fact, there were some instances in which a rise in the inotropic state with tachycardia could not be discerned even when end-diastolic size was held constant (fig. 7).

Heart Failure. As with ouabain, the inotropic effects of increasing heart rate were greater in the failing than in the nonfailing heart. Increasing heart rate from 120 to 240 beats/min did not affect systolic RVP but decreased RV end-diastolic and end-systolic SL by 0.92 ± 0.09 and 0.43 ± 0.05 mm, respectively. RV $dP/dt/P$ rose by 41 ± 4% from a control of 24 ± 4 sec$^{-1}$ and peak V rose by 51 ± 3% from a control of 15 ± 3 mm/sec (fig. 5); these increases were greater ($P < 0.05$) on an absolute as well as a percentage basis from those that occurred in the nonfailing heart.

Discussion

The purpose of this investigation was to determine the effects of chronic heart failure on the inotropic response to a cardiac glycoside and to an augmentation of cardiac frequency. In view of the previously demonstrated striking effects of general anesthesia on the cardiovascular response to a variety of interventions,\textsuperscript{19, 20, 25, 29} it was felt important to perform these studies in the conscious state. The right ventricle is more suitable than the left for production of chronic heart failure. However, previous studies on right ventricular function and contractility have been conducted largely in open chest anesthetized preparations\textsuperscript{2, 4, 6} or in isolated papillary muscle strips.\textsuperscript{7, 11} An extremely limited number of studies on right ventricular performance have been carried out in the conscious organism.

In order to conduct the present investigation in the normal and failing right ventricles of conscious dogs, techniques for assessment of left ventricular function previously utilized in our laboratory\textsuperscript{19, 20, 25} were modified to provide a measure of right ventricular pressures and dimensions, $dP/dt$, and velocity of myocardial fiber shortening. An index of right ventricular dimensions was obtained by continuously measuring the distance between a pair of opposing miniature ultrasonic crystals implanted in the right ventricle (fig. 1). The right ventricular segment length was continuously differentiated to provide an instantaneous rate of change of dimensions, i.e., velocity of myocardial fiber shortening. These measurements, in combination with those of intraventricular pressure, $dP/dt$ and $dP/dt/P$, were used for an instantaneous and continuous assessment of right ventricular function and contractility.

Ouabain exerted only a slight inotropic effect on the right ventricle of the normal, conscious dog, but a much greater inotropic effect both in magnitude and duration was elicited in these same dogs after chronic right heart failure had been induced. Both the absolute and relative increases in velocity and $dP/dt/P$ with ouabain were greater in the presence of heart failure. In addition, while ouabain altered the extent of systolic dimensional shortening only slightly in the nonfailing heart, in the presence of heart failure, the extent of myocardial shortening per stroke increased, principally due to a much greater reduction of end-systolic size; i.e., a more complete systolic ejection. Thus, cardiac glycosides exert a potent inotropic ac-

Figure 6

Figure 7

Response to elevation of heart rate (HR) on RV segment length (SL) (top); velocity (V) (second panel); pressure (P) (third panel); and $dP/dt$ (fourth panel) while maintaining end-diastolic size constant with saline infusion (right panel). In this example a rise in contractility with pacing was not observed.
tion in the chronically failing heart as well, as had been previously observed,19 in the heart acutely depressed by a general anesthetic, or by large doses of propranolol. This difference between the response of the normal and chronically failing heart appears to be due in part to the higher baseline level of the inotropic state in the normal, conscious animal. In addition, the effects of ouabain in the intact animal are complex.

For instance, it is known that ouabain increases arterial pressure and the rate of rise of the pressure pulse, thereby stimulating baroreceptor reflexes which might attenuate the inotropic effects.30, 31 This mechanism may not be present to as great an extent in heart failure,32, 33 after general anesthesia,29 or after propranolol pretreatment, since all of these conditions alter the extent of reflex and autonomic control of the circulation.29, 32, 33

As was the case with ouabain, increasing cardiac frequency elicited only a minor increase in myocardial contractility in the nonfailing heart. The positive inotropic effect of increasing heart rate, i.e., the Bowditch staircase or the force-frequency relation, has been thought to be a substantial one; studies in isolated muscle strips or in anesthetized preparations have indicated that the elevation of contraction frequency exerts a potent inotropic effect.8–18 In this investigation it was also found to have a relatively potent inotropic effect in the chronically failing right ventricle, but as was the case for cardiac glycosides, it produced only a minor effect on the normal right ventricle. The possibility was considered that the reduction in end-diastolic cardiac dimensions which occurs with increasing cardiac rate30 may have masked a portion of the inotropic effect of tachycardia. However, when end-diastolic dimensions were maintained constant by rapid saline infusion, while frequency was increased, the increases in dP/dt/P and velocity were still small (19% and 21%, respectively) and in fact were less than occurred with tachycardia after heart failure had been induced. Furthermore, the possibility that a substantial positive inotropic response could not be observed with these techniques when end-diastolic size was reduced, as occurred with pacing was considered. However, when end-diastolic size was reduced to the same extent as with pacing, by the administration of isoproterenol, a drug with well recognized powerful inotropic action, five-fold increases in dP/dt/P were observed, indicating that the techniques employed in this study are sensitive to inotropic increases even in the presence of markedly diminished preload. Furthermore, end-systolic size fell more than end-diastolic with isoproterenol, reflecting a greater extent of myocardial fiber shortening per stroke, as would be expected with a potent positive inotropic influence. In contrast, in the normal heart with induced tachycardia and ouabain the extent of myocardial fiber shortening per stroke changed only slightly; in fact, with induced tachycardia, stroke excursion actually fell.

In conclusion, cardiac glycosides and elevating cardiac frequency each exert relatively minor positive inotropic actions in the nonfailing right ventricle of the healthy conscious animal, when compared with effects in isolated cardiac muscle preparations or anesthetized animals. The positive inotropic actions of these stimuli are also much more profound in the same animals after chronic congestive right heart failure was induced.

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