Characterization of the Frequency-Force Relationship in the Dog Atrium In Situ

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ABSTRACT

Isometric developed tension and rate of development of tension in the in situ atrium of the anesthetized dog have been shown to increase consistently with increasing heart rate over a wide range. This study thus definitively demonstrates that both the ascending and descending staircase effects occur in the dog atrium in situ. At high cardiac rates the velocity of force development may increase without a change in the extent of force development. These changes were independent of variations in aortic pressure, intactness of beta-adrenergic receptors, level of cardiac catecholamine stores, cardiac innervation, or changes in coronary flow. The character of the frequency-force relationship was found to be markedly influenced by isolation of the heart with its concomitant depression of contractility.

ADDITIONAL KEY WORDS

atrial treppe ventricular treppe catecholamines and atrial treppe atrial contractility ventricular contractility coronary flow during treppe

Since the classical description by Bowditch (1) in 1871 of a stepwise increase in the force of contraction of the frog ventricle associated with increasing heart rate, this phenomenon has been frequently investigated. In 1902 Woodworth (2) described in the dog ventricle an opposing reaction in which a transient decrease in contractile strength occurred with increasing heart rate. Reviews by Leonard and Hajdu (3) and by Koch-Weser and Blinks (4) have aided greatly in clarifying current knowledge concerning the frequency-force relationship in cardiac muscle.

Although this relationship has been described in isolated atrial and ventricular muscle and in ventricular muscle of blood-perfused hearts in situ (4), the phenomena has been reported not to occur in the intact atrium. Williams and co-workers (5) concluded that the classic Bowditch staircase appears to play no role in the function of the atrium in the intact dog between rates of 150 and 240/min.

The present study was undertaken to study the frequency-force relationship over a wide physiologic range of heart rates in the dog heart in situ and to investigate possible underlying mechanisms which may contribute to the over-all atrial response to a change in the frequency of stimulation.

Methods

Two different preparations were utilized: the open chest but otherwise intact animal and an isolated blood-perfused heart in which the left ventricle performed no external work. The following description applies to both preparations. A more complete description of the isolated heart will be given later in this section.

Mongrel dogs, weighing 12 to 25 kg, were anesthetized with pentobarbital sodium (30 mg/kg) and thoracotomies were performed during positive pressure respiration. The sinoatrial node was crushed and the heart rate was varied by stimulation through bipolar electrodes sewn to the atrial appendage. Atrial force was monitored with an 11-mm strain gauge arch (6) sutured to either the left (12 dogs) or the right (8 dogs) atrium. Sutures extended through the entire thickness of the muscle and were set so as to give an approximately 50% stretch from initial length of the muscle segment beneath the arch. The

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first derivative of atrial force (dF/dt) was obtained using an RC differentiating circuit. In some experiments ventricular force was measured with a strain gauge arch equipped with an adjustable foot to alter fiber length. Aortic pressure was recorded in all experiments from a catheter inserted into the carotid artery and advanced into the aortic arch. Atrial pressure was obtained in three experiments from a catheter passed through the atrial appendage or through a pulmonary vein into the atrial chamber. Ventricular pressure was measured through a multihole metal cannula. All pressures were recorded using Statham P23Gb transducers; continuous recordings were made on a Sanborn multichannel oscillograph Model 350.

In 2 animals beta-adrenergic receptor blockade was produced by intravenous propranolol in a dose of 0.5 mg/kg. Adequacy of block was ascertained by the absence of tachycardia or of an increase in atrial and ventricular force or just in ventricular force when 20 μg of norepinephrine were administered intravenously.

Two dogs were studied that had undergone cardiac denervation 6 weeks previously employing the method of Cooper et al. (7). Adequacy of denervation was tested on the day of the experiment using intravenous norepinephrine and Unitensen (cryptenamine) as described by Willman and co-workers (8). Tissue catecholamine levels were determined using Crout’s (9) modification of the trihydroxyindole method of Lund (10).

The second experimental preparation employed was a blood perfused isolated heart. The heart was isolated by ligating the superior vena cava, inferior vena cava, azygos vein, hilum of both lungs, brachiocephalic artery, left subclavian artery, and the aortic arch just below the left subclavian artery. Coronary inflow was maintained by perfusing the isolated aortic segment with blood from the femoral arteries of an intact anesthetized dog. The chamber of the left ventricle received only Thebesian flow and this was drained through an apical catheter. The aortic valve was kept closed by maintaining the coronary perfusion pressure above the very small pressure developed by the essentially empty left ventricle. The chamber of the right ventricle received only coronary venous outflow and this was drained through a catheter inserted through the azygos vein. This outflow was continuously monitored with a Shipley-Wilson rotameter (11) and was then returned to the jugular veins of the perfusion dog. The rotameter was calibrated by timed collection into a graduated cylinder.

Transient and steady-state changes in the force of contraction and dF/dt were measured over the widest possible range of heart rates in each preparation. Only those changes that occurred in the presence of a stable resting tension were analyzed. In 3 experiments, 10% calcium gluconate was infused into the coronary inflow of the isolated heart at variable rates and frequency-force relationships were determined at several levels of plasma calcium. Calcium determinations were performed colorimetrically using a Technicon autoanalyzer and all reported levels are total coronary venous plasma calcium concentrations.

In 5 animals, sustained postextrasystolic potentiation of the atria was achieved by the technique of coupled pacing using bipolar atrial electrodes with an interstimulus interval of approximately 150 msec.

In 3 animals, the cross sectional area of the muscle segment beneath the atrial strain arch was estimated by dividing the wet weight of the segment by its length during the experiment (5). The strain gauges were calibrated by suspending known weights from 1 foot of the arch while the arch was held with its long axis oriented vertically.

Resting tension was estimated by comparing the baseline tension with the gauge sewn on the atrium with the recording after 1 foot of the gauge had been cut from the atrium.

The following data are representative of results from 15 in situ and 5 isolated heart preparations.

Results

IN SITU PREPARATION

Figure 1 (upper) is illustrative of the changes that occurred with alterations in frequency of contraction. When heart rate was increased from 75 to 130 beats/min, there occurred an initial transient decrease in developed force of the right ventricle (RVF) and left atrium (LAF) as well as a decrease in the rate of atrial force development (dF/dt). This was followed by an increase in these variables until both the developed force and the maximum dF/dt stabilized at higher values than were present at the lower rate. The same general pattern of response is seen in the recording of right ventricular pressure (RVP), except that it did not return to the control value. During this sequence of events aortic pulse pressure decreased but mean aortic pressure declined only slightly. The reverse sequence of events in the same preparation when heart rate was decreased from...
Influence of increasing heart rate from 92 to 120/min, on right atrial force (RAF) of an in situ heart. AP = aortic pressure, RAF = right atrial pressure.

136 to 63 beats/min is shown in Figure 1 (lower). There was an initial increase, followed by a stepwise decrease, in RVF, LAF, and dF/dt. Similar changes were seen in RVP.

The influence of increasing heart rate on right atrial force (RAF), right atrial pressure (RAP), and aortic pressure (AP) of a heart in situ is depicted in Figure 2. A striking initial decrease in RAF occurred on the first beat after increasing heart rate before AP had changed. This was followed by a stepwise increase in RAF at a time when AP was at a lower, relatively constant level. RAP showed little change. This figure illustrates that even though substantial transients may occur when frequency of stimulation is varied, the steady-state values for developed force may not show large differences. Both the transient changes and new steady-state increases in developed force and maximum dF/dt were obtained in all animals studied independently of the directional changes in aortic or atrial pressures.

Figure 3 is a plot of steady-state values for developed force of the right ventricle, left atrium, and maximum atrial dF/dt as functions of heart rate and interval between beats. Both the developed force and the maxi-
mum rate of force development of the atrium increase with increasing heart rate over the low frequency ranges until an optimum frequency is reached. Further increases in rate then produce a progressive fall in force and maximum dF/dt. The ventricular curve shows a similar biphasic picture. The optimum frequency as measured in this experiment was the same for both left atrial force and maximum dF/dt. This was not, however, the general rule. In 8 of 11 in situ preparations in which measurements were made at rates greater than 160/min, the optimum frequency for maximum dF/dt was higher than that for developed force. Thus, at high heart rates the velocity of force development may increase with frequency when developed force no longer does. The optimum frequency for ventricular developed force was approximately 15 to 20 beats/min higher than that for atrial developed force in the 6 animals in which simultaneous measurements were made.

Data were obtained from 3 animals before and after vagotomy. Although vagotomy increased both force and maximum dF/dt, the characteristic frequency-force relationship was always observed when rate was increased after this intervention.

In the 2 animals with propranolol-induced, beta-adrenergic receptor blockade, there was no alteration in the basic characteristics of the frequency-force relationship. Both animals showed a slight fall in developed force and maximum dF/dt after propranolol.

Figure 4 shows that rate-induced changes in right ventricular force, left atrial force, and maximum atrial dF/dt occur in the chronically denervated catecholamine-depleted canine heart. When the rate was decreased from 150 to 63/min, both transient and steady-
Influence of decreasing heart rate from 150 to 63/min on RVF, LAF, and atrial dF/dt of an in situ chronically denervated heart. AP = aortic pressure, stim = stimulation artifact. Tissue catecholamines in μg/g of wet tissue: RV 0.04, LA 0.16.

Figure 4 illustrates that postextrasystolic potentiation (another form of interval-dependent change in force and velocity of contraction) can be seen in the in situ atrium as well as the ventricle. In this heart a spontaneous premature atrial contraction occurred and the following beat showed marked potentiation of right ventricular force, right atrial force, and maximum atrial dF/dt. The same phenomenon was observed in the chronically denervated heart.

In this preparation coronary flow, background catecholamine level, and neural influences could be maintained relatively constant. Figure 6 is a typical illustration of the very large frequency-induced change of left atrial force and atrial dF/dt when rate was first increased from 96 to 200/min and then decreased to 96/min. Although coronary flow changed slightly in this experiment, in other experiments the same changes in atrial force occurred without consistent changes in coronary blood flow.

The difference between the in situ and isolated heart in response to a change in frequency is more clearly demonstrated in Figure 7. These plots of steady-state left atrial force as a function of heart rate were obtained in the same animal before and after isolation.
FIGURE 5
Influence of a spontaneous premature atrial systole on RVF, RAF, and atrial dF/dt of an in situ heart. AP and RVP also shown.

The two uppermost curves (triangles) are from the in situ heart and illustrate the biphasic character of the atrial frequency-force relationship in the open chest animal as shown previously in Figure 3. The lowest curve (open circles) is from the same animal approximately 55 min later (25 min after isolation of the heart). Note the marked decline in developed force at any given rate. Instead of being biphasic, the curve is now monophasic with a steadily increasing developed force with increasing rate. Similar curves were found in all cases when maximum dF/dt was plotted instead of developed force. The remaining curve (Fig. 7, closed circles) depicts the frequency-force pattern in the isolated heart during positive inotropic stimulation with an infusion of 10% calcium gluconate which raised the total plasma calcium from 9.05 to 13.49 mg%. All portions of the curve are shifted upwards with a tendency to level off at the highest rate; there was no decrease with increasing rate. These results are typical of 3 experiments in which data were obtained before and after isolation of the heart. In the two other isolated heart preparations, monophasic frequency-developed force curves were found but no data were obtained prior to isolation of the heart. The marked fall in atrial force, maximum atrial dF/dt, and also ventricular force after isolation can be seen as soon as steady-state hemodynamic conditions have been reestablished, that is, as early as 15 min after isolation.

The influence of coupled pacing of the atrium on left atrial force, atrial dF/dt, and left ventricular force is shown in Figure 8. The interval between coupled stimuli was 145 msec and heart rate was 120/ min. The uppermost tracing is coronary perfusion pressure and the lowest tracing is coronary flow. The delay in transmission of the second stimulus to the ventricle possibly accounts in part for its smaller increase in force when compared with the atrium. Similar results were obtained in 4 other animals in which coupled pacing was achieved. Although there would appear to be an increase in resting tension of the atrium with coupled pacing in Figure 8, this was not a consistent finding.

Resting tension was estimated in 6 animals and averaged 46.3% of total tension. In 2 animals, estimated resting tension was actually greater than developed tension; one explanation for this is that these muscle segments were on the descending limb of their length-tension curves. Results from these 2 experi-
Influence of changing heart rate from 96 to 200 to 96/min on left atrial force (LAF) and atrial dF/dt (the dots indicate peaks in this tracing) of an isolated heart. CF = coronary flow.

Discussion

The association of a faster and stronger ventricular contraction with increasing heart rate over a wide physiologic range is of importance to the intact animal in terms of meeting the increased metabolic demands of stress such as exercise, with little encroachment on the Frank-Starling mechanism. The

In 3 experiments, cross-sectional area of the muscle segment studied was estimated and developed force expressed in grams per square millimeter. These values ranged from 0.7 to 6.6 g/mm² with the heart rates studied.

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Influence of sustained postextrasystolic potentiation produced by coupled pacing of the atrium on left ventricular force (LVF), LAF, and atrial dF/dt of an isolated heart. (The dots indicate peaks for the LAF and dF/dt tracings.) Stimulation delay is 145 msec. PP = coronary perfusion pressure, CF = coronary flow.

FIGURE 8

shortened systole is of further importance in maintaining diastolic coronary flow and in allowing time for adequate relaxation between beats despite the higher heart rate. It is reasonable to assume that the atrium might also have similar characteristics, that is, increase its force and velocity of contraction when its frequency is increased. The present study definitively demonstrates that this is the case and also that staircase, both ascending and descending, occurs in the atrium in situ. The data further demonstrates that the changes in atrial contractility induced by changing heart rate can occur independently of changes in aortic pressure and coronary blood flow in the beta-receptor blocked or chronic denervated heart. The frequency-force curve for the dog atrium in situ in the majority of dogs in the present study showed an optimum frequency of approximately 130/min with higher rates associated with no change or small fall in steady-state developed force. The mechanism accounting for this decline in steady-state developed force and maximum dF/dt with increasing heart rate at high frequencies is not known but may be related to the decreased duration of the active state (4). The phenomenon can be seen in isolated heart muscle preparations (4), but it has been suggested that its presence in this situation is due to inadequate oxygenation at high levels of activity. It would seem unlikely that this would be the case in the present study, since the phenomenon was observed in the presence of a high coronary perfusion pressure and as rapidly as...
temperature equilibration allowed for a steady baseline after the strain gauge was sewn on either the atrium or ventricle. The possibility exists that the fall in steady-state developed force with increasing heart rate might be due to inadequate time for complete relaxation between beats, even though evidence for this could not be seen in the tension tracings. The use of a strain gauge to measure muscle performance imposes certain limitations. Among these is that it measures the changes in performance of only the muscle segment attached to the gauge. Also the atrial muscle fibers are not oriented in a single plane so that the changes in tension shown by the gauge represent a mean change of all these fibers. Despite these limitations, however, there is no reason to believe that the changes in force indicated by the gauge are not at least qualitatively representative of the whole atrium.

The failure of Williams and co-workers (5) to find any consistent change in the steady-state force of the intact dog atrium when its rate changed between 150 and 240 beats/min can probably be related to several factors. In the range studied by them, a slight fall in developed force with increasing heart rate might be expected in most animals. The fact that they observed an increase, a decrease, or no change in steady-state force development in different animals over this range is explicable in terms of animal variability of optimum frequency and of the state of contractility when frequency was varied. Since Bowditch's experiments on alterations in the staircase phenomenon with various drugs (1), there have been repeated demonstrations of variation in the frequency-force relationship with different inotropic interventions (4). It is well established that there is an upper limit for contractility that can be reached by various interventions (4). In a hypodynamic heart, ascending staircase becomes more pronounced, while in a vigorously contracting heart it can be abolished or even a fall in developed force may occur with increasing heart rate over certain frequencies. Thus, over any range of increasing heart rate, the over-all response must be considered in terms of ascending staircase, descending staircase and the inotropic state at the time when rate is changed. It is of interest that although steady-state force and/or dF/dt may not show large changes after increasing heart rate (see Fig. 2), ascending staircase may nonetheless still be present.

The modification of the frequency-force relationship after isolation of the heart offers a striking example of the extent to which this relationship may be influenced by the contractile state of the myocardium. The decline in force and maximum dF/dt for any given frequency after isolation was somewhat surprising in its extent as well as its rapidity of onset. It is unlikely that catecholamine depletion could either occur this quickly or cause such a large depression. It is also unlikely that coronary flow to the isolated muscle segment was limiting performance after isolation, since severe depression still occurred in 1 animal immediately after isolation despite a coronary perfusion pressure of greater than 125 mm Hg. Several interesting possibilities remain. Does the tension that the myocardium develops play a role in determining the state of contractility and could the isometric force developed by a small segment of muscle be influenced by the degree of tension development in the remainder of the muscle? Evidence for an increase in contractility with increased afterload in the heart in situ is, of course, readily available, (12-14) and the factor initiating the positive inotropic effect could well be the increase in developed tension. Thus, in the present study, the decrease in isometric developed force and dF/dt of the atrial muscle segment after isolation might be in part due to the large fall in the tension which the remainder of the myocardium develops after isolation and gravity drainage of all chambers. Finally, the abolition of sympathetic discharge to the heart which occurs after isolation may account for a large part of the decline in contractility which was seen in the isolated heart.

The studies on both the chronic denervated and beta-receptor blocked hearts demonstrate...
that the basic mechanism underlying the frequency-force relationship of the myocardium is not altered by these interventions. Further, the results from the cardiac denervated animals show that atrial treppe can be found despite depletion of cardiac catecholamines.

In the present experiments no attempt was made to stimulate with only barely suprathreshold stimuli. It is therefore possible that some release of norepinephrine might have occurred secondary to stimulation (15). The finding of a pattern of treppe, in both propranolol-blocked and cardiac-denervated dogs, that was in all respects similar to that in the innervated and nonblocked animals demonstrates that the positive staircase shown cannot be attributed to an increased release of catecholamines with increased heart rate. These data extend to the intact ventricle and atrium Koch-Weser's results on the force-frequency relationship in catechol-depleted and beta-receptor blocked kitten papillary muscles (15).

The results presented demonstrate, therefore, that changing the frequency of stimulation can influence the extent and rate of force development of the intact dog atrium. This is not unexpected in that, under conditions of stress, the positive inotropic ventricular response to tachycardia alone is considerable. The more forceful as well as faster left atrial contraction could aid considerably in the animal's ability to successfully meet any sudden change in overall metabolic demands, by enhancing ventricular filling while pulmonary capillary pressure is maintained at a level well below that at which edema formation would begin.

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