Effects of Heart Rate on the Dynamics of Force Development in the Intact Human Ventricle

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SINCE Bowditch’s classic description of the effect of stimulation frequency on the force of contraction of the frog ventricle,¹ the relations between contractile force and heart rate have been studied in many animal species.²⁻⁷ Indeed, Kruta⁸ has suggested that “the basic mechanism of inotropic effects of all changes of frequency (or even of one single interval) exists in all vertebrate myocardial preparations, and is one of the most striking and important features of the mechanical response of the heart muscle.” It has been observed, however, that the detailed nature of the inotropic response to changing frequency varies between species,⁴⁻⁷ and while the influence of changing heart rate in man has been studied in relation to hemodynamics,⁹⁻¹² no direct measurements of the force-frequency relationships in the intact human heart have been made. In the present study, the effects of alterations in heart rate on the dynamics of force development were determined in the human right ventricle in the course of corrective intracardiac operations. Coronary blood flow was not interrupted, and this obviated the limitations of myocardial oxygen supply encountered with in vitro preparations. It was observed that velocity of myocardial contraction and the duration of contraction varied inversely with heart rate as in other species. In the human heart, however, force of contraction was found to change little with large alterations in rate.

Methods

Walton-Brodie strain-gauge arches¹³ were sutured to the right ventricles of 11 patients at the time of cardiac operations. Five patients had atrial septal defects, three aortic valve disease, and three ventricular septal defects. Halothane anesthesia (0.5 to 1.0%) was generally employed. The segment of myocardium beneath the gauge was stretched approximately 50% beyond its initial length, and the deflections produced by the strain gauge were registered on a photographic oscillograph at appropriate recording paper speeds. Changes in heart rate were produced by electrical stimulation of the right ventricle in nine patients and of the right atrium in two. Bipolar electrodes were used to deliver a 5 ma D.C. stimulus of 2-msec duration. The heart rate was increased in increments of 10 to 20 beats per minute (from a rate just above the spontaneous one) to a rate of 95 to 170. With the highest rates, inadequate relaxation of the muscle segment was apparent in some force tracings, and the records at these rates were not utilized in the analysis. In five patients, Prostigmine 0.5 or 1.0 mg was given intravenously prior to the study in order that frequencies of less than 70 per minute could be explored. Measurements of the changes in peak tension or force of contraction (PT), the time to peak tension (TTPT), and the maximum rate of change of force (df/dt) were made from high resolution tracings obtained after each change in stimulation frequency, and when a constant level of contractile force was apparent. In some patients, maximum df/dt was also measured electrically with an R-C differentiating circuit (time constant 1.0 msec). The strain-gauge arches were not calibrated in terms of absolute force, and tension was expressed as millimeters of deflection, indicative of relative changes only. The transient changes in force which occurred in the first beats following abrupt changes in rate were also analyzed. Observations were made in nine patients after the institution of total cardiopulmonary bypass, while all systemic venous and coronary sinus return was diverted from the right ventricle. In the remaining two patients the circulation was intact. Ten patients were receiving maintenance doses of digoxin (0.25 to 0.5 mg/day), while

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the glycoside had not been given to the remaining patient.

**Results**

The effects of increasing frequencies of stimulation on peak myocardial contractile force, time to peak force, and maximum df/dt in all 11 patients are summarized in figure 1, and portions of representative records are reproduced in figures 2 and 3. As heart rate was progressively increased from an average of 72 beats per minute (range 53 to 110) to an average of 142 per minute (range 95 to 170), only small changes in peak contractile force were observed, averaging $-9 \pm 6.5\%$ (SE) between the extremes of heart rate. In every patient, as heart rate was increased, a substantial and progressive increase in the maximum df/dt was noted (average $+42 \pm 10\%$). The increase in df/dt was always accompanied by a significant decrease in the time to peak contractile force, averaging $-31 \pm 3.5\%$.

The transient effects of sudden changes in the frequency of stimulation are illustrated in figures 4 through 6. When heart rate was increased abruptly (fig. 4), the force of the subsequent contraction was of lesser magnitude than the control beat, and force then gradually rose to reach a value approximating the control one within 5 to 10 contractions.

![Figure 1](http://circ.ahajournals.org/content/XXXIII/6/946/F1.large.jpg)

*Figure 1*

The effects of increasing frequency of contraction on the maximum rate of right ventricular force development (df/dt) (top panel), the peak force developed (middle panel), and the time required to reach maximum force (bottom panel).

![Figure 2](http://circ.ahajournals.org/content/XXXIII/6/946/F2.large.jpg)

*Figure 2*

Typical tracings of right ventricular force development illustrating the effects of increasing frequency of contraction (panels 1 to 4). Below each panel are shown frequency of contraction (H.R.), the time required to reach peak tension (TTPT), rate of force development (df/dt) which is indicated by the dashed line on the tracing, and the peak tension developed (PT). With an increase in contraction frequency, df/dt and TTPT varied inversely, while PT decreased slightly.
The time to peak force also decreased with the first contraction after rate was increased, that is, with the first contraction with a shorter interval between stimuli (fig. 6, upper panel); thereafter, the time to peak force remained relatively constant. In contrast, the peak df/dt increased only slightly with this first contraction, but then increased progressively, reaching a constant value at approximately the same time as the contractile force. With a sudden decrease in frequency of stimulation (fig. 5) the reverse process was noted. The force of the first contraction at the slower frequency was generally increased, and in subsequent beats force gradually declined to the control value (figs. 5 and 6, lower panels). The time to peak force increased with the first contraction at the slower frequency, that is, with the first contraction occurring after the longer interval, and showed relatively little change thereafter. Maximum df/dt, however, diminished gradually with each contraction until contractile force again reached a constant level.

In this patient PT increased slightly with increasing heart rate while large inverse changes in df/dt and TTPT occurred. Designations same as in figure 2.

The transient effects of an abrupt increase in contraction frequency (arrow) on right ventricular force and the rate of change in force. Stimulation frequencies are indicated on the tracing.
Thus, the duration of contraction (time to peak force) changed abruptly with a change in the interval of time between contractions, while \( \frac{df}{dt} \) and peak force reached a steady state over the course of several contractions. The responses described were the same whether the right ventricle or the right atrium was stimulated, and the results in patients

\[ \text{Figure 5} \]

The transient effects of an abrupt decrease in contraction frequency on right ventricular contractile force, and the rate of change in force (\( \frac{df}{dt} \)). Stimulation frequencies are indicated on the figure.

\[ \text{Figure 6} \]

High speed tracings illustrative of the transient changes associated with a sudden increase in the frequency of contraction from 75 to 118 beats per minute (above) or a decrease from 118 to 75 beats per minute (below). Right ventricular force, the rate of force development, and the ECG are shown. The vertical arrows indicate the changes in frequency. The brackets above each force deflection indicate the time from the onset of that contraction to the time at which peak contractile force was achieved.
studied during cardiopulmonary bypass did not differ from those obtained in patients in whom the circulation was intact. Similarly, responses in the undigitalized patient did not differ from those in the patients receiving therapeutic doses of digoxin.

Discussion

The results of the experiments described indicate that changes in the contraction rate of the intact human heart, over a wide physiological range, have little effect on the peak contractile force of the ventricle. Alterations of heart rate, however, produce major changes in the maximum rate of force development and the absolute time between the onset of contraction and the development of peak force. The significance of these findings are best appreciated when they are related to the basic mechanics of muscular contraction. The peak force that can be generated in an isometric contraction depends upon two factors: the rate with which force is developed, and the time provided for this force to be generated. According to Hill,14 muscle contraction reflects the interaction of an active contractile element and a passive elastic component while rate of force development depends on the properties of both of these components. The contractile element is characterized by its force-velocity relation, and its speed and force of contraction are the mechanical reflections of the intensity of active state.15,16 Since the series' elastic component of heart muscle does not vary with inotropic interventions,17,18 increments in the rate of force development will reflect an increase in the maximum intensity of the active state.14 However, the peak force developed also depends upon the duration of the active state. It has been demonstrated that the time to peak isometric force varies directly with the duration of the active state,15,18 and thus changes in intensity and duration are reflected in changes in peak df/dt and the time to peak force, respectively. The determinants of the peak force of a contraction, therefore, can be analyzed by measurements of the maximum df/dt and time to peak force of that contraction. These considerations apply if the duration of the active state is limited, and the force developed is always less than the maximum force which the contractile elements are capable of developing, conditions which exist with rhythmic contractions of heart muscle.

In isolated heart muscle preparations, both a "force staircase,"1 where a progressive rise in the force of contraction with increasing heart rate occurs, and a "reverse staircase,"4,5 where force of contraction falls with increasing heart rate, have been described. In the present studies of intact human hearts, a positive force staircase was not generally observed. With a progressive increase in rate, however, the maximum rate of force development, reflecting an increased velocity of contraction, was consistently augmented. This increased velocity, with a concomitant decrease in the time to peak force, and resultant constant force development, has been termed a "velocity staircase."18,19 Such a velocity staircase has also been noted in human heart muscle studied in vitro,20 and the significance of this experimental finding is reinforced by the present observations made in intact hearts in which coronary perfusion was normal. Since the maximum rate of force development and time to peak force vary directly with the intensity and duration of the active state, respectively, an increase in heart rate in man appears to result in an increase in the intensity of the active state. However, the concomitant shortening of the duration of active state is of such magnitude that peak force remains essentially unchanged. In descriptive terms, the "Bowditch or force staircase" and the "reverse staircase" are balanced in human heart muscle such that net force development remained relatively constant.4

The relations between duration and intensity of the active state and peak force described above are those recorded during a steady state after an increase in rate. However, when the frequency of stimulation was suddenly changed, transient changes in peak force were noted. These changes apparently resulted from the different times
required for the intensity and duration of the active state to reach their final constant values. A sudden decrease in heart rate resulted in an immediate increase in peak force, since the duration of the active state increased without a significant change in its intensity. In succeeding contractions, the intensity of the active state gradually decreased while the duration remained relatively constant, and peak force returned to control levels (fig. 6). With a sudden increase in the frequency of stimulation, the reverse was observed; the duration of the active state decreased immediately, intensity did not change, and peak force decreased. As the intensity of the active state decreased in succeeding beats, duration was unchanged, and peak force gradually fell. These findings suggest that the duration of active state depends primarily upon the interval between contractions on a beat-to-beat basis, while changes in the intensity of active state occur more slowly.

The usual force-frequency relationship observed in most animals is abolished if the myocardium is operating near the upper limit of its contractile response. The absence of a demonstrable force staircase in this study, therefore, might be interpreted as indicating that the hearts of these patients, under the conditions of the investigation, were operating at the peaks of their contractile states. This was not the case, however, since force increased after a sudden decrease in rate and contractile force rose more than 50% in the two patients to whom isoproterenol was administered at the conclusion of the study. In isolated muscle preparations it has been demonstrated that digitalis glycosides also will prevent increased force with increased rate, but only when toxic doses of digitalis are employed. The patients studied displayed no evidences of digoxin toxicity, and since the results were similar in the patient not receiving digoxin, the absence of a force staircase cannot be attributed to the glycoside.

The present study demonstrates that in man an increase in heart rate produces significant changes in the intensity and duration of the active state. The inverse relation of these changes in active state results in an increase in the velocity of contraction but does not affect peak contractile force. The basic mechanisms by which the duration and intensity of the active state are altered inversely, so that peak force remains constant, are not apparent. However, the existence of such mechanisms permits the human ventricle to shorten its period of contraction when increases in heart rate occur, conserving the diastolic filling time without reducing the force of its contraction.

Summary

The effects of heart rate on the dynamics of force development in the ventricle were studied in the intact human heart. In the course of corrective cardiac operations, Walton-Brodie strain-gauge arches were sutured to the right ventricles of 11 patients. The peak contractile force, the time to peak force, and the maximum rate of change of force (df/dt) were determined at various heart rates, produced by electrical stimulation of the right atrium or right ventricle. As the rate was increased, from an average of 72 to 145 per minute, no significant change in peak contractile force was observed. The peak df/dt, however, increased with each increment in heart rate, and the time to peak force decreased. This inverse relationship between peak df/dt and time to peak force accounts for the constancy of the peak force observed within several contractions after heart rate was changed. Also, since df/dt and the time to peak force reflect the intensity and duration of the active state, respectively, an inverse relationship between these factors is implied. Sudden changes in heart rate were associated with transient changes in peak contractile force, attributable to differences in the rates with which peak df/dt and time to peak force reached new constant values.

In man, therefore, a "velocity staircase," rather than a "force staircase," occurs with changes in heart rate. The possession of this mechanism apparently permits the human
ventricle to maintain its force of contraction and preserve the duration of diastolic filling with increases in rate.

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