Influence of Acute Alterations in Heart Rate and Systemic Arterial Pressure on Echocardiographic Measures of Left Ventricular Performance in Normal Human Subjects

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SUMMARY
To study the effects of acute alterations in heart rate and systemic arterial pressure on the mean velocity of left ventricular circumferential fiber shortening (Vcf) and on mean posterior wall velocity (Vpw), we performed ultrasound studies in 25 normal human subjects between the ages of 21 and 29 years. When heart rate was augmented by the administration of intravenous atropine from 64 ± 2.2 (SEM) to 98 ± 2.7 beats/min, mean normalized Vcf increased from 1.22 ± 0.05 to 1.38 ± 0.06 circumferences (circ)/sec (P < 0.001). Mean normalized Vpw increased from 0.76 ± 0.03 to 0.89 ± 0.04 sec⁻¹ (P < 0.001). Mean Vcf and mean Vpw uncorrected for end-diastolic diameter increased in a similar fashion (P < 0.01). After atropine administration, systemic arterial pressure was augmented by means of a phenylephrine infusion in 23 subjects by an average of 39 mm Hg (range 20–50 mm Hg). During the phenylephrine infusion, average heart rate decreased from 96 ± 2.6 to 91 ± 3.1 beats/min (NS), while mean normalized Vcf declined from 1.38 ± 0.06 to 1.09 ± 0.05 circ/sec (P < 0.001) and normalized Vpw from 0.89 ± 0.04 to 0.65 ± 0.04 sec⁻¹ (P < 0.001). Nonnormalized velocities exhibited similar alterations (P < 0.01). We conclude that in the normal human subject mean Vcf and mean Vpw are sensitive to acute alterations in heart rate and systemic arterial pressure. Thus, when ultrasound measures are used for serial assessment of left ventricular performance, the level of heart rate and systemic arterial pressure at which studies are obtained must be considered. Further, the sequential use of atropine and phenylephrine, as described in this study, provides an experimental model for the evaluation of the effects of drug treatment and other interventions on left ventricular performance in man.

ECHOCARDIOGRAPHY provides a useful noninvasive method for the assessment of left ventricular performance in man. Although a number of ejection phase indices, including the ejection fraction (EF),¹,² mean normalized posterior wall velocity (Vpw),¹ and the normalized mean rate of circumferential fiber shortening (Vcf),¹,² can be derived from the echocardiogram, there is little information concerning the acute effects of alterations in heart rate and systemic arterial pressure on these measures. Therefore, to evaluate the influence of acute changes in heart rate and blood pressure on these echocardiographic ejection phase indices of left ventricular performance, we studied normal subjects in the basal state and after the administration of atropine and phenylephrine.

Methods

Study Design
The study population consisted of 25 normal human volunteers (ten women and 15 men). They were between the ages of 21 and 29 and had no cardiovascular disease as assessed by history and physical examination. The resting electrocardiogram was within normal limits in all subjects. After the subjects were familiarized with the procedures, and informed consent was obtained, an intravenous infusion of 5% dextrose and water was begun using a scalp vein needle inserted into a forearm vein. A baseline echocardiogram and measurements of heart rate and systemic arterial pressure (cuff sphygmonanometer) were obtained. Subsequently, atropine was administered intravenously in a quantity sufficient to raise the heart rate at least 30 beats/min or until a maximum of 1.5 mg had been given. When the heart rate and systemic arterial pressure were stable for at least ten minutes, a second echocardiogram was obtained. At this point, with the heart rate response to increased arterial pressure blocked by atropine, phenylephrine (10 mg diluted in 250 ml of 0.9% NaCl) was infused in 23 subjects over 5 to 10 minutes in a quantity sufficient to raise the systolic arterial pressure approximately 40 mm Hg. With systolic pressure held at this level, a third echocardiogram was ob-

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tained and the infusion terminated. The total volume of fluid used in the entire study did not exceed 50 ml.

Recording Technique

Echocardiograms were recorded with a Picker ultrasonoscope utilizing a 2.25 MHz, 1.27 cm transducer focused at 7.5 cm, with a repetition rate of 1000 impulses/sec. The output signal was recorded on a Honeywell Visicorder Oscillograph model 1856. Each patient had an electrocardiogram recorded simultaneously with the echogram. Echocardiograms were obtained with the subjects in the supine or partial left lateral decubitus position. The transducer was placed at the third or fourth intercostal space, just to the left of the sternum. With the transducer directed posteriorly and slightly medially, the mitral valve echo was identified; the transducer was then rotated inferolaterally to obtain echoes from the endocardial surfaces of the left side of the interventricular septum and the posterior wall. Left ventricular dimensions were measured at the level of the posterior mitral valve supporting apparatus, which was identified by its continuity with the posterior mitral valve leaflet on scanning superiority and medially. Fragments of the mitral valve leaflet echoes were also frequently observed (fig. 1). In nine subjects a carotid arterial pulse tracing was obtained simultaneously with the echocardiogram. The carotid arterial pulse tracing was obtained with a bell held manually over the carotid artery and connected by an air-filled tube to a Statham P23Db strain gauge manometer.

Measurements and Calculations

Left ventricular dimensions were measured between the endocardial surfaces of the posterior wall and the left side of the septum (fig. 1A). The end-diastolic dimension (EDD) was measured at a point on the time motion scan coincident with the peak of the R wave of the simultaneously recorded ECG. The end-systolic dimension (ESD) was defined as the smallest distance separating the left ventricular endocardial surfaces even if the points of maximum excursion were not exactly opposed. In addition, the left ventricular ejection time (ET) was measured as the length of time from the peak of R wave to the maximum anterior excursion of the left ventricular posterior wall, less 50 msec for the preejection period. Subsequently, it became technically feasible to record a carotid arterial pulse tracing simultaneously with the echocardiogram. The validity of the earlier method of measuring ET was confirmed for the basal state and under conditions of altered heart rate and afterload in the nine subjects in whom ET was obtained from the simultaneously recorded carotid arterial pulse tracing, and the method of determining the ejection time in no way altered the results obtained. In addition, the sex of the subject did not influence the results of the study.

The mean rate of circumferential fiber shortening (mean Vcf [cm/sec]) was calculated as:

$$\frac{(EDD - ESD)}{ET}$$  \[1\]

The mean normalized Vcf (circumferences [circ]/sec) was calculated as:

$$\frac{(EDD - ESD)}{ET \times EDD}$$  \[2\]

![Figure 1](http://circ.ahajournals.org/)

A) Calculation of ultrasound dimensions in the control state. For the beat illustrated control values were: Mean Vcf = 1.22 circ/sec; mean Vpu = 0.79 sec; EF = 0.75. The heart rate was 66 beats/min. EDD = end-diastolic dimension; ESD = end-systolic dimension; PWE = posterior wall excursion; ET = ejection time; CH = chordae tendineae; MV = anterior leaflet of mitral valve; CPT = carotid arterial pulse tracing; ECG = electrocardiogram. B) After the administration of atropine, the heart rate has increased to 116 beats/min; mean Vcf has increased to 1.42 circ/sec and mean Vpu to 1.05 sec; EF declined slightly to 0.71. C) During phenylephrine administration after atropine the systolic arterial pressure was augmented by 42 mm Hg. The heart rate declined by only 5 beats/min to 111 beats/min, but mean Vcf decreased 0.98 circ/sec, mean Vpu to 0.76 sec; and EF to 0.63, all of which are below control values.
Mean posterior wall velocity (mean Vpw [cm/sec]) was calculated as:
\[ \text{PWE/ET} \] [3]
where PWE = total excursion of the posterior wall endocardium during systole.

Mean normalized Vpw (sec\(^{-1}\)) was calculated as:
\[ \text{PWE/ET} \times \text{EDD} \] [4]
Ejection fraction (EF%) was calculated by the cube method:
\[ (\text{EDD}^2 - \text{ESD}^2)/\text{EDD}^3 \] [5]
All data were analyzed by the paired Student’s t-test with the aid of a Sigma III computer.

**Results**

**Increasing Heart Rate**

After the administration of atropine, heart rate increased in the 25 subjects from an average of 64 \( \pm \) 2.2 (SEM) to 98 \( \pm \) 2.7 beats/min (\( P < 0.001 \)). Systemic systolic arterial pressure also increased from 114 \( \pm \) 2.0 to 122 \( \pm \) 2.2 mm Hg (\( P < 0.001 \)). Mean normalized Vcf increased from 1.22 \( \pm \) 0.05 to 1.38 \( \pm \) 0.06 circ/sec (\( P < 0.001 \), fig. 2). Mean Vcf uncorrected for end-diastolic diameter increased in a similar fashion from 5.9 \( \pm \) 0.2 to 6.4 \( \pm \) 0.3 cm/sec (\( P < 0.01 \)). The increase in mean Vcf was paralleled by an increase in mean normalized Vpw from 0.76 \( \pm \) 0.03 to 0.89 \( \pm \) 0.04 sec\(^{-1}\) (\( P < 0.001 \), fig. 3). Nonnormalized mean Vpw increased similarly from 3.7 \( \pm \) 0.1 to 4.1 \( \pm \) 0.2 cm/sec (\( P < 0.01 \)). EDD also decreased significantly from 49.1 \( \pm \) 1.0 to 47.1 \( \pm \) 1.2 mm (\( P < 0.01 \)), consistent with decreased filling time associated with a higher heart rate. EF did not change significantly. Individual patient data are detailed in table 1 and a typical response to increased heart rate is depicted in figure 1B.

**Increasing Afterload**

Following the infusion of phenylephrine, systolic arterial pressure increased in 23 subjects by an average of 39 mm Hg (range 20 to 50 mm Hg). The slight decrease in mean heart rate from 98 \( \pm \) 2.7 to 91 \( \pm \) 3.1 beats/min was not significant. Mean normalized Vcf declined from 1.38 \( \pm \) 0.06 to 1.09 \( \pm \) 0.05 circ/sec (\( P < 0.001 \), fig. 2). Nonnormalized mean Vpw also decreased from 6.4 \( \pm \) 0.3 to 5.4 \( \pm \) 0.2 cm/sec (\( P < 0.001 \)). Similarly, mean normalized Vpw declined from 0.89 \( \pm \) 0.04 to 0.65 \( \pm \) 0.04 sec\(^{-1}\) (\( P < 0.001 \), fig. 3), as did nonnormalized mean Vpw (4.1 \( \pm \) 0.2 vs 3.2 \( \pm \) 0.2 cm/sec, \( P < 0.001 \)). EDD also increased significantly from 47.1 \( \pm \) 1.3 to 49.6 \( \pm \) 1.1 mm (\( P < 0.001 \)) and EF showed a significant decline from 76 \( \pm \) 1.0 to 71 \( \pm \) 2.0% (\( P < 0.01 \)). For individual patient data, see table 1. A typical response to increased systemic arterial pressure is shown in figure 1C.

**Discussion**

**Effects of Alterations in Heart Rate**

A considerable body of evidence published since the well-known studies of Bowditch7 and Woodworth8 suggests that an augmentation of heart rate, exclusive of alterations produced by exercise, exerts a positive inotropic effect on the myocardium. Studies carried out on excised strips of myocardium,9-11 isolated hearts,12 anesthetized preparations,13-17 and human subjects18,19 have indicated that tachycardia enhances the contractile state of the myocardium. In previous studies of the normal conscious dog, however, Noble and his colleagues20 could not substantiate such an effect, and more recently Higgins and coworkers demonstrated only a modest augmentation of left ventricular dP/dt in response to atrial pacing in the nor-
Table 1

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\[ P < 10^{-4} \text{ NS} < 10^{-6} < 10^{-6} < 10^{-6} < 10^{-6} < 0.01 < 10^{-4} \]

Our results in normal human subjects are in accord with the latter study. After an increase in heart rate averaging 34 beats/min, mean normalized Vcf determined by the ultrasound technique increased by an average of 13%. Similar increases were observed in mean normalized posterior wall velocity. The results were similar when nonnormalized values were compared. These alterations in ejection phase indices were observed despite a modest increase in average systemic systolic arterial pressure of 8 mm Hg. Such an increase in systolic pressure would be expected to reduce mean Vcf and Vpw (see below). EDD was significantly reduced, but it has been recently shown, both in the conscious dog and in normal human subjects, that acute alterations in EDD have little effect on mean Vcf. Previous studies have shown that beat-to-beat alterations in loading conditions during atrial fibrillation in man may exert a profound influence on ejection phase indices of left ventricular performance. The influence of chronic increases in heart rate are not known, but data obtained in normal infants indicate that average mean Vcf is higher than in adults with slower basal heart rates. It should be emphasized that the augmentation of heart rate in our study was quite modest (55% above control values) relative to other reports. In the study of Mahler and coworkers, an average increase of 65 beats/min (71% above control values) produced an augmentation of mean Vcf of 22%. By contrast, Higgins and coworkers observed no increase in mean Vcf despite an increase of 126 beats/min which was 134% above control values. The results of the latter study may have been influenced by the use of epicardial rather than endocardial ultrasound crystals. Thus, our data demonstrate that in normal human subjects important alterations in left ventricular performance occur over the range of heart rates usually considered to be within the physiologic range.

Whether the positive inotropic effect of an increase in cardiac rate is the result of catecholamine release merits consideration. Mahler and his colleagues observed no alteration in the inotropic response to tachycardia after a blocking dose of propranolol. In a further group of nine normal subjects whom we
studied separately, oral propranolol in a dose sufficient to depress the basal heart rate by 17% had no effect on the increase in mean Vcf observed during intravenous atropine administration. These observations appear to exclude the possibility that some of the alterations in contractile state were the result either of reflex or of generalized catecholamine release induced by atropine administration. Our data are also consistent with the hypothesis that the enhanced inotropic state produced by tachycardia is unrelated to the release of beta-adrenergic agonists.38

The importance of parasympathetic activity (vagal tone) in the control of left ventricular performance under normal circumstances is a matter of some controversy.29 Although the cholinergic innervation of human and canine ventricular myocardium is sparse,80 experimental studies have indicated that under some circumstances the parasympathetic nervous system may exert a distinct tonic negative inotropic influence31 which can be released by cholinergic blockade with atropine.32 Such a release could have been at least partially responsible for the increase in left ventricular performance after atropine observed in the present study, and our data do not allow exclusion of this possibility.

Effects of Alterations in Systemic Arterial Pressure

Experimental studies have documented a reduction in the extent and velocity of myocardial shortening as the resistance to ejection is increased.36,37 However, the effects of acute augmentation of systemic arterial pressure (increase in afterload) have not been well-defined in the normal human subject. During investigations in normal human subjects an increase in stroke work in response to an angiotensin infusion has been reported,44-46 but this has not been a uniform finding.37,38 The inotropic effects of angiotensin itself and the variability of the ventricular function curves obtained by O'Rourke and coworkers in the pre-instrumented dog36 suggest that this substance may not be a suitable one for this purpose. A consistent observation of the latter investigators, however, was that stroke excursion declined in response to an acute increase in afterload. Recently, this response was confirmed by Mahler and coworkers, who described a 32% decline in mean Vcf in the normal conscious dog in response to an increase in systemic systolic pressure averaging 211 mm Hg.49 Our data in normal human subjects are in agreement with these observations. After a more modest increase in systemic systolic arterial pressure, averaging 39 mm Hg, and with
reflex adjustments in heart rate prevented by the prior administration of atropine, mean normalized Vcf and Vpw exhibited significant decreases (21 and 27%, respectively). The same measures uncorrected for left ventricular end-diastolic diameter changed in a similar fashion. The effects of chronic pressure loading, such as that produced by systemic arterial hypertension, have not been defined, but experiments in conscious dogs indicate that mean Vcf remains within the normal range once adaptation to a chronic pressure overload has occurred. 40

Whether influences other than those produced by an acute increase in afterload affected our results deserves comment. An acute withdrawal of sympathetic tone does not seem to be operative, since in normal conscious dogs subjected to a similar experiment, alterations in left ventricular dP/dt were minimal. 28 It is unlikely that phenylephrine itself exerted a depressant effect on the left ventricular myocardium, since this drug in large doses behaves as a beta-adrenergic agonist, 41 and direct intracoronary injection of phenylephrine leads to augmented flow. 42 Thus, the reduction in internal shortening velocities produced by increasing the resistance to ejection cannot be attributed either to alterations in the autonomic nervous system or to a direct pharmacologic effect of drug administration.

Ultrasound Assessment of Left Ventricular Performance

The usefulness of determinations of mean Vcf for separating normal from abnormal subjects has been well-demonstrated, 37, 43 and the application of the concept of normalized internal shortening velocity to echocardiographic measurements has proved to be a fruitful approach. 3-6, 37 The present study confirms observations reported in the normal conscious dog 23 and in a small number of patients 37 and extends them to normal human subjects in sinus rhythm. These data indicate that internal shortening velocities are useful in the characterization of left ventricular performance in man provided that acute alterations in heart rate and systemic arterial pressure do not occur. Thus, when serial ultrasound studies of left ventricular performance are employed to assess the effects of interventions such as surgical procedures, consideration must be given to the levels of heart rate and systemic arterial pressure at which the recordings are obtained. Finally, the sequential use of atropine and phenylephrine, as described in this study, provides an experimental model in the human subject for assessing the effects of drug therapy and other interventions on left ventricular function in man.

References
8. Woodworth RA: Maximal contraction, "staircase" contraction, refractory period, and compensatory pause of the heart. Am J Physiol 8: 213, 1902
9. Date AS: The stair case phenomenon in ventricular muscle. J Physiol 75: 1, 1832

23. MAHLER F, ROSS J Jr, O’ROURKE RA, COVELL: Effects of changes in preload, afterload and inotropic state on ejection and isovolumic phase measures of left ventricular contractility in the conscious dog. Am J Cardiol 35: 626, 1975


26. SAHN DJ, VAUCHER Y, WILLIAMS DE, FRIEDMAN WR: Echo distinction of left-to-right shunts from non-structural heart disease (NHD) in infancy. Circulation 50 (suppl III): III-16, 1974


32. STANTON HC, VICK RL: Cholinergic and adrenergic influences on right ventricular contractility in the dog. Arch Int Pharmacodyn Ther 176: 233, 1968


34. ROSS J Jr, BRAUNWALD E: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. Circulation 29: 739, 1964


43. KARLIER JS, GAULT JH, ECKBERG D, MULLINS CB, ROSS J Jr: Mean velocity of fiber shortening: A simplified measure of left ventricular contractility. Circulation 44: 323, 1971

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