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Alexander Harley, … , C. Frank Starmer, Joseph C. Greenfield Jr.

J Clin Invest. 1969;48(5):895-905. https://doi.org/10.1172/JCI106048.

Research Article

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Pressure-Flow Studies in Man. An Evaluation of the Duration of the Phases of Systole

ALEXANDER HARLEY, C. FRANK STARMER, and JOSEPH C. GREENFIELD, JR.

From the Department of Medicine (Division of Cardiology), Duke University Medical Center, Durham, North Carolina 27706, and the Veterans Administration Hospital, Durham, North Carolina 27705

ABSTRACT This study was designed to assess the independent effects of stroke volume and heart rate on the phases of systole and other selected hemodynamic parameters. By means of the pressure gradient technique instantaneous blood pressure and flow were recorded in the ascending aorta at fixed ventricular rates in five patients with complete heart block and in four patients with atrio-ventricular dissociation induced by ventricular pacing. Because of the variable contribution of atrial systole to ventricular filling, a wide range of stroke volumes were observed at each heart rate. The results indicate that the duration of ejection bears a close direct linear relationship to stroke volume while heart rate has only a weak but independent relation. On the other hand, the duration of total systole is related chiefly to the heart rate but stroke volume exerts an important independent effect. In a given patient, both duration of ejection and pulse pressure reflect changes of stroke volume and the product of the duration of ejection and the pulse pressure shows a good correlation with the stroke volume.

INTRODUCTION

Previous studies in man of the relationships between heart rate, stroke volume, and other hemodynamic parameters such as the phases of systole, have been limited by the methodological difficulties encountered in measuring phasic blood flow. The recent development of the pressure gradient technique has made it possible to measure aortic blood flow and pressure continuously in the intact human subject. Furthermore, it has been difficult in man to vary either stroke volume or heart rate independently without altering the inotropic environment. In patients with atrio-ventricular dissociation, beat to beat differences in stroke output occur which are due primarily to variations in the atrial contribution to ventricular filling and not changes in myocardial contractility. Since these changes in stroke volume are often considerable, a wide range of stroke volumes is available at a constant rate. Ventricular pacing techniques permit study of several fixed heart rates in a given patient. By means of these methods the independent effects of heart rate and stroke volume on various hemodynamic parameters can be examined without resorting to exercise, drugs, or other maneuvers which alter both stroke volume and heart rate simultaneously.

This report presents an analysis of hemodynamic data obtained at a variety of controlled heart rates from five patients having complete heart block and four patients with atrio-ventricular dissociation induced by right ventricular pacing.

METHODS

Pressure-flow recordings were obtained in five adult male patients with complete heart block admitted to the Durham Veterans Administration Hospital for the treatment of Stokes-Adams attacks. In addition, similar studies were carried out in four patients with normal sinus rhythm in whom atrio-ventricular dissociation was produced by pacing the right ventricle. These studies were performed during the course of routine diagnostic cardiac catheterization. The informed consent of each patient was obtained before catheterization.

All five patients with heart block presented with Stokes-Adams attacks. Three gave a history of a remote myocardial infarction and one had mild angina pectoris. Only two pa-

Dr. Harley's present address is Cardiac Department, Bristol General Hospital, Bristol, England.

Dr. Greenfield is the recipient of a Career Development Award (1-K3-HE-28,112), from the U. S. Public Health Service.

Received for publication 15 October 1968 and in revised form 20 January 1969.

TABLE I
Clinical Data

Patient	Diagnosis*	Age	Blood pressure	Resting heart rate	N. Y. Ht. class‡	Cardiomegaly	Previous cardiac failure	Digitalis
		yr	*mm Hg*	*beats/min*				
H. B.	CHB–SAA	62	120/80	38	2			
H. W.	CHB–SAA	59	110/70	36	2			
A. S.	CHB–SAA IHD	58	140/90	38	1	+		
C. S.	CHB–SAA IHD	74	170/80	45	2	+	+	
N. T.	CHB–SAA IHD	70	120/80	40	1			
D. L.	Normal	44	110/70	73	0			
A. H.	IMH	35	100/60	85	1	+		+
J. S.	IMH	54	130/90	90	2	+	+	+
E. A.	IMH Hypertension	42	160/110	80	2	+	+	+

* Abbreviations used in diagnosis column: CHB = complete heart block; SAA = Stokes-Adams attacks; IHD = ischemic heart disease; IMH = idiopathic myocardial hypertrophy.
‡ N. Y. Ht. Class = New York Heart Association Classification.

tients had radiographically evident cardiac enlargement. One patient gave a history suggestive of cardiac failure but showed no clinical evidence of decompensation at the time of study. Of the four patients in normal sinus rhythm, three had clinical evidence of generalized myocardial disease and were receiving digitalis. Two of these patients had been in cardiac failure a few weeks before the study; one patient was receiving reserpine for hypertension. The fourth patient was investigated to exclude hypertrophic sub-aortic stenosis but no hemodynamic evidence of cardiovascular disease was found. Other pertinent clinical data describing these patients are listed in Table I.

Phasic blood pressure and flow were recorded in the ascending aorta by the pressure gradient technique (1). This method is based on an approximate linear solution of the Navier-Stokes equations of fluid motion (1, 2). It is assumed that the vessel is uniform, that the velocity profile is flat, and that there is little radial acceleration of fluid (1). These conditions appear to be reasonably satisfied in the ascending aorta. Experimental evaluation of the pressure gradient technique has been carried out in a phasic flow generator where the "true" flow was known and in the dog aorta where the "true" was measured with an electromagnetic flowmeter. These studies demonstrated that the pressure gradient technique can be used to provide a reasonable measure of phasic blood flow (2, 3). The manometric accuracy requirements and the calibration procedures used in this laboratory to obtain valid phasic flow measurements in man have been detailed elsewhere and will be outlined only briefly (3).

A specially designed 6.5 French double-lumen catheter,[1] having lateral pressure taps separated by 4 cm was inserted via the femoral artery into the ascending aorta and used to measure the blood pressure at two points. An analog computer [2] was used to obtain the pressure difference and to continuously compute phasic blood flow. Pressure from the distal lumen of the catheter was also recorded. Heart rate (HR) was controlled with right ventricular pacing by means of a No. 5 bipolar pacing catheter, placed at the apex of the right ventricle under fluoroscopic control, and a battery pulse generator.[3] The electrocardiogram was recorded throughout the study. All data were recorded on an optical recorder [4] at a paper speed of 100 mm/sec and on an electromagnetic tape system.[5]

Both phasic blood pressure and flow were measured continuously in all patients for approximately 2 min during the control period and at each different heart rate. In this study the lowest pacing rate which suppressed other ventricular activity was chosen as control. After each increase in heart

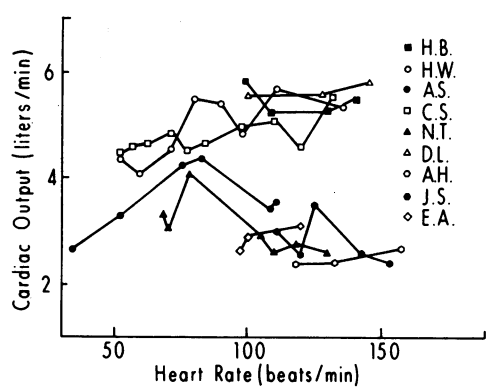

FIGURE 1 Cardiac output computed from the mean stroke volume at each ventricular rate studied in the nine patients.

[1] U. S. Catheter & Instrument Corp., Glens Falls, N. Y.
[2] Model 3400 Analog Computer, Systron-Donner Corporation, Concord, Calif.
[3] Model 5840 Medtronic, Inc., Minneapolis, Minn.
[4] Model 4568 Hewlett-Packard Co., Palo Alto, Calif.
[5] Model 3955 Hewlett-Packard Co., Palo Alto, Calif.

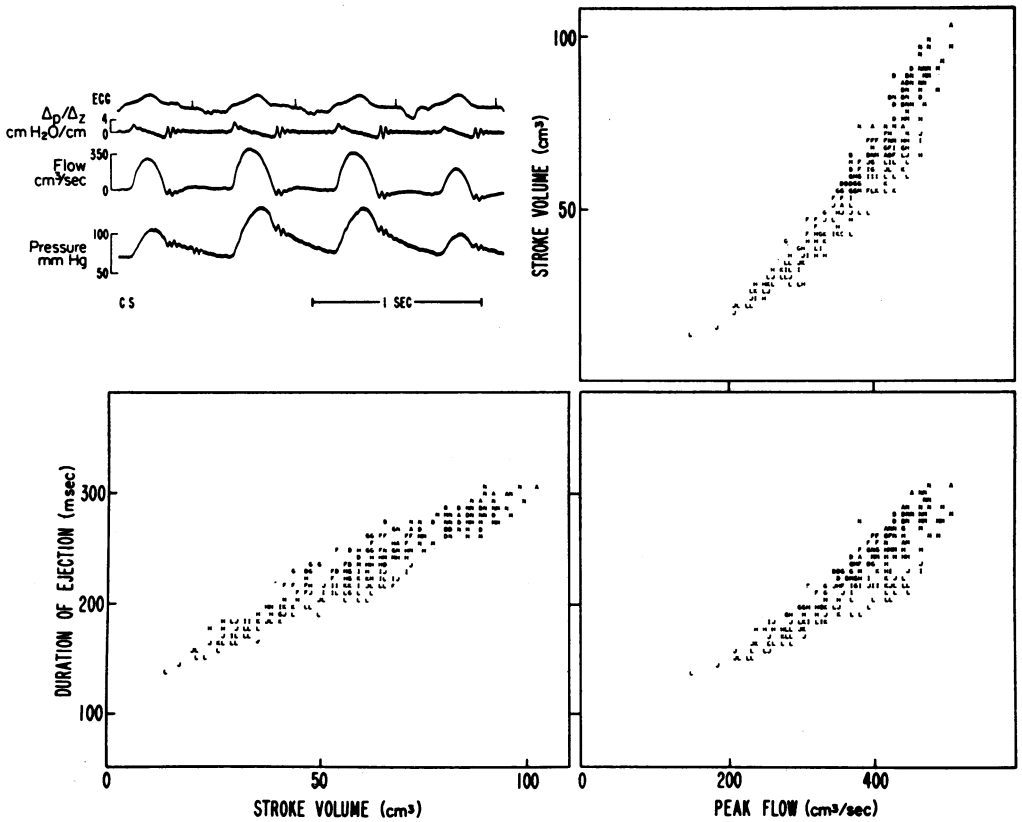

FIGURE 2 Data from patient C. S. showing a representative recording (upper left). The interrelationships of stroke volume, peak flow, and duration of ejection at a variety of ventricular rates appear in the other three panels. The plots were printed by the digital computer. Each letter represents a different period of recording and in most cases a separate ventricular rate. Since many points fell in the same position on the plots, less than the total number of data points appear (350 for C. S.). When two points occupied the same position, the plotting program selected the point represented by the letter latest in the alphabet.

TABLE II

Correlation of Stroke Volume with Phases of Systole

Patient	Stroke volume, range	A. Duration of ejection: Duration of ejection, range	A. Duration of ejection: Regression equation	A. Duration of ejection: Correlation coefficient, *r*	B. Duration of systole: Duration of systole, range	B. Duration of systole: Regression equation	B. Duration of systole: Correlation coefficient,
	cm³	*msec*			*msec*		
H. B.	23–86	145–245	DE = 115 + 1.56 SV ±8.6	0.95	300–395	DS = 279 + 1.24 SV ±10.0	0.91
H. W.	19–100	165–280	DE = 107 + 1.80 SV ±9.4	0.96	320–415	DS = 283 + 1.42 SV ±14.7	0.85
A. S.	24–92	160–310	DE = 106 + 2.26 SV ±10.8	0.96	355–450	DS = 327 + 1.45 SV ±13.3	0.88
C. S.	13–103	140–315	DE = 111 + 2.04 SV ±11.3	0.97	340–500	DS = 324 + 1.61 SV ±17.7	0.88
N. T.	5–67	95–260	DE = 119 + 2.03 SV ±16.6	0.93	345–465	DS = 368 + 1.12 SV ±22.4	0.70
D. L.	26–75	160–210	DE = 123 + 1.20 SV ±6.2	0.93	290–350	DS = 276 + 0.88 SV ±12.7	0.68
A. H.	5–34	105–215	DE = 91 + 3.19 SV ±8.8	0.93	310–380	DS = 319 + 0.98 SV ±11.8	0.50
J. S.	5–58	90–190	DE = 94 + 1.92 SV ±11.7	0.91	280–310	DS = 281 + 0.47 SV ± 8.1	0.52
E. A.	8–64	110–200	DE = 117 + 1.62 SV ±11.7	0.92	335–380	DS = 347 + 0.34 SV ±13.0	0.32
All	5–103	90–315	DE = 106 + 2.00 SV ±16.0	0.94	280–500	DS = 305 + 1.50 SV ±36.0	0.69

In Tables II to VIII, the duration of ejection (DE) and systole (DS) are given in milliseconds, stroke volume (SV) in cubic centimeters, and heart rate (HR) in beats per min. Each regression equation is followed by the standard error.

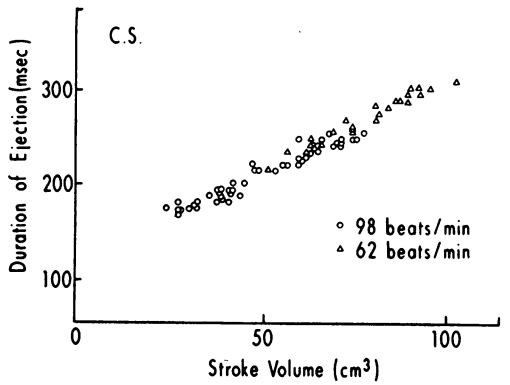

FIGURE 3 Relationship of stroke volume and duration of ejection at two ventricular rates in patient C. S.

rate an equilibration period of 2 min was allowed before pressure-flow recordings were made.

From 90 to 350 separate heart beats were analyzed from each patient. Tracings in which the stroke volume (SV) varied widely at each heart rate were chosen. The systolic, diastolic, and pulse pressure were measured directly from pressure recordings. Planimetric integration of the flow tracing was used to obtain stroke volume. Zero flow was assumed to be present at the end of diastole. Peak flow was measured as the maximal amplitude of the flow recording. The duration of systole (DS) was measured as the period from the onset of the QRS complex of the electrocardiogram to the end of forward flow. Since ventricular pacing was used, the onset of the QRS complex was frequently indistinct and was arbitrarily taken to occur 40 msec after the pacing artifact. Duration of ejection (DE) was taken as the duration of forward flow. The pre-ejection period (PEP) was calculated by subtracting the duration of ejection from the duration of systole. Mean systolic flow was obtained by dividing the stroke volume by the duration of ejection. All computations of the data including the statistical analysis and plotting were carried out on a digital computer.[6]

RESULTS

A total of 1050 separate heart beats were analyzed. These provided a wide range of stroke volumes for each

[6] Model 1130, International Business Machines, New York.

TABLE III

Correlation at Individual Heart Rates in Patient C. S.

No. of beats studied	Heart rate	Stroke volume, range	A. Duration of ejection: Duration of ejection, range	A. Duration of ejection: Regression equation	A. Duration of ejection: Correlation coefficient, r	B. Duration of systole: Duration of systole, range	B. Duration of systole: Regression equation	B. Duration of systole: Correlation coefficient, r
	beats/min	*cm³*	*msec*			*msec*		
26	52	66–100	250–315	DE = 158 + 1.54 SV ±8.8	0.84	450–500	DS = 396 + 0.94 SV ±7.6	0.74
30	57	56–97	225–290	DE = 145 + 1.56 SV ±8.4	0.89	440–480	DS = 400 + 0.72 SV ±9.5	0.63
36	62	51–103	220–315	DE = 130 + 1.92 SV ±8.2	0.95	420–480	DS = 369 + 1.13 SV ±7.6	0.88
31	71	46–91	225–285	DE = 147 + 1.59 SV ±7.8	0.93	425–465	DS = 390 + 0.77 SV ±6.8	0.82
27	77	42–74	200–270	DE = 117 + 2.09 SV ±9.5	0.92	410–445	DS = 377 + 0.92 SV ±6.0	0.85
33	84	39–68	190–270	DE = 116 + 2.10 SV ±11.0	0.87	400–450	DS = 360 + 1.11 SV ±8.5	0.78
49	98	24–77	170–260	DE = 122 + 1.83 SV ±6.5	0.97	375–455	DS = 361 + 0.82 SV ±7.8	0.85
35	110	24–71	165–235	DE = 125 + 1.63 SV ±4.8	0.98	365–410	DS = 362 + 0.60 SV ±3.5	0.92
47	120	16–69	140–235	DE = 119 + 1.71 SV ±6.0	0.97	360–400	DS = 353 + 0.62 SV ±4.9	0.88
37	132	13–66	140–220	DE = 120 + 1.53 SV ±4.8	0.98	340–380	DS = 341 + 0.56 SV ±4.6	0.89

TABLE IV

Correlation of Heart Rate with Duration of the Phases of Systole in Each Patient

Patient	A. Duration of ejection: Regression equation	A. Duration of ejection: Correlation coefficient, r	B. Duration of systole: Regression equation	B. Duration of systole: Correlation coefficient, r
H. B.	DE = 309 − 1.02 HR ±22.8	0.61	DS = 448 − 0.94 HR ±17.8	0.67
H. W.	DE = 304 − 0.98 HR ±15.3	0.88	DS = 454 − 0.93 HR ±8.7	0.95
A. S.	DE = 337 − 1.46 HR ±12.9	0.94	DS = 477 − 0.93 HR ±14.1	0.86
C. S.	DE = 351 − 1.35 HR ±24.6	0.82	DS = 537 − 1.33 HR ±12.8	0.94
N. T.	DE = 320 − 1.30 HR ±31.8	0.66	DS = 532 − 1.24 HR ±15.9	0.87
D. L.	DE = 258 − 0.63 HR ±12.6	0.68	DS = 413 − 0.77 HR ±9.7	0.83
A. H.	DE = 229 − 0.57 HR ±21.6	0.41	DS = 423 − 0.62 HR ±8.5	0.78
J. S.	DE = 222 − 0.64 HR ±20.9	0.42	DS = 344 − 0.39 HR ±7.8	0.60
E. A.	DE = 202 − 0.38 HR ±23.0	0.20	DS = 456 − 0.92 HR ±7.5	0.84
All	DE = 338 − 1.30 HR ±27.0	0.82	DS = 525 − 1.40 HR ±28.0	0.83

of the three to ten different ventricular rates in each patient.

The cardiac output calculated from the mean stroke volume for each heart rate is illustrated in Fig. 1. The output showed no specific trends between 70 and 150 beats/min. The variations in cardic output in a given patient appeared to be due primarily to a more or less favorable pattern of timing between atrial and ventricular contraction. The cardiac output was low in the three patients with myocardial disease and less than normal at most rates in two of the patients with heart block.

A representative pressure-flow recording obtained from patient C. S. appears in the upper left panel of Fig. 2. Note that the contour of the flow pulse changes little with different stroke volumes. In none of the patients did the shape of the flow pulses vary systematically over the range of heart rates and stroke volumes studied.

Table II A lists the data relating the duration of ejection to the stroke volume for each patient. The correlation coefficients (Table II A) ranged from $r = 0.91$ to $r = 0.97$ with $r = 0.94$ for the pooled data. Plots of these data appeared to be linear in every patient except N. T. and E. A. in whom the duration of ejection increased at a slightly slower rate in the upper range of stroke volume. A typical plot of duration of ejection and stroke volume is shown in the lower left panel of Fig. 2. The relationship between duration of ejection and stroke volume was also examined separately at each heart rate in each patient. A plot of these data from patient C. S. at two representative ventricular rates is shown in Fig. 3. Table III A shows the results of the regression of duration of ejection on stroke volume at all 10 heart rates in patient C. S. Note that the slopes and intercepts (Table III A, column 5) of these regression equations coincide reasonably well with the equation relating duration of ejection to stroke volume over the whole range of heart rates. Similar findings were noted in the other subjects.

The correlation of heart rate with duration of ejection for each patient was generally poor (Table IV A). To examine the effect of heart rate alone (i.e. to exclude the effect of stroke volume) duration of ejection and heart rate were plotted and analyzed for heart rates grouped by stroke volume decades, i.e., 20–30 cm³, 30–40 cm³, etc. Fig. 4 illustrates the relationship of duration of ejection and heart rate for each of three stroke volume decades from patient C. S. Table V A gives the regression equations for this relationship for each of seven stroke volume decades from the same patient. In the other subjects these plots also fell into more or less parallel lines, the slopes of which did not vary systematically between the higher and lower stroke volume decades. The effects of heart rate and stroke volume on duration of ejection were further explored by multiple regression analysis. Table VI A shows the multiple regression of duration of ejection on stroke volume and heart rate. The standardized regression coefficient shown in Table VI A indicate that stroke volume alone accounted for most of the observed variation of duration of ejection in each subject.

Duration of systole was examined in the same manner

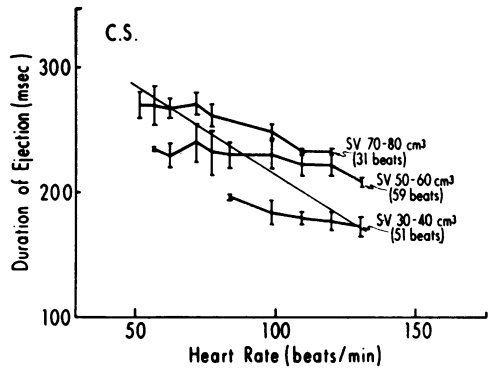

FIGURE 4 Relationship of heart rate and duration of ejection for three stroke volume decades in patient C. S. The vertical lines represent the range of duration of ejection at each ventricular rate. The heavy lines connect the median ejection time at each ventricular rate in each stroke volume decade. The thin line represents the linear regression of duration of ejection and heart rate over the entire range of stroke volumes.

TABLE V

Correlation of Heart Rate with Duration of Phases of Systole for Each Stroke Volume Decade in Patient C. S.

Stroke volume, range	Heart rate, range	No. of beats	A. Duration of ejection		B. Duration of Systole	
			Regression equation	Correlation coefficient, *r*	Regression equation	Correlation coefficient, *r*
cm³	*beats/min*					
20–30	98–132	29	DE = 226 − 0.54 HR ±8.1	0.62	DS = 489 − 1.01 HR ±5.9	0.90
30–40	84–132	51	DE = 232 − 0.47 HR ±5.6	0.75	DS = 474 − 0.84 HR ±5.2	0.91
40–50	71–132	45	DE = 246 − 0.41 HR ±11.4	0.55	DS = 486 − 0.88 HR ±7.5	0.91
50–60	57–132	59	DE = 257 − 0.34 HR ±8.6	0.68	DS = 494 − 0.91 HR ±6.1	0.96
60–70	57–132	62	DE = 286 − 0.49 HR ±11.7	0.71	DS = 504 − 0.92 HR ±9.0	0.92
70–80	52–120	31	DE = 300 − 0.49 HR ±8.1	0.75	DS = 515 − 0.97 HR ±10.1	0.87
80–90	52–71	49	DE = 305 − 0.33 HR ±8.9	0.24	DS = 524 − 1.01 HR ±10.0	0.55

TABLE VI
Multiple Correlation of Stroke

Patient	A. Duration of ejection				
	Regression equation	Correlation coefficient, r		Standardized regression coefficients*	
		Stroke volume	Stroke volume and heart rate	Heart rate	Stroke volume
H. B.	DE = 163.7 + 1.40 SV − 0.35 HR	0.95	0.97	−0.21	+0.85
H. W.	DE = 167.8 + 1.32 SV − 0.36 HR	0.96	0.98	−0.32	+0.71
A. S.	DE = 196.0 + 1.42 SV − 0.50 HR	0.96	0.97	−0.39	+0.60
C. S.	DE = 166.9 + 1.68 SV − 0.39 HR	0.97	0.98	−0.23	+0.79
N. T.	DE = 180.6 + 1.75 SV − 0.52 HR	0.93	0.95	−0.25	+0.79
D. L.	DE = 163.3 + 1.01 SV − 0.25 HR	0.93	0.96	−0.28	+0.79
A. H.	DE = 141.2 + 3.03 SV − 0.34 HR	0.93	0.96	−0.24	+0.88
J. S.	DE = 137.9 + 1.80 SV − 0.33 HR	0.91	0.93	−0.21	+0.86
E. A.	DE = 131.6 + 1.66 SV − 0.15 HR	0.92	0.93	−0.08	+0.91

* In order to compare the partial regression coefficients relating DE or DS to both HR and SV, standardized regression coefficients were used (4). These standardized coefficients result when each regression coefficient is adjusted for its individual variation. Writing the multiple regression equation in terms of the standardized coefficients indicates how many standard deviations the dependent variable (DE or DS) changes with a one standard deviation change in any independent variable (HR or SV). Using the magnitude of the standardized coefficients in this manner gives one a measure of the sensitivity of the predicted variable to standardized changes in the predicting variables.

‡ The correlation coefficient for the single regression given for heart rate or stroke volume depending on which variable accounted for most of the variation of duration of ejection or systole.

as the duration of ejection. Table II B lists the data relating the duration of systole to the stroke volume for each patient. The correlations (Table II B) range from $r = 0.32$ to $r = 0.91$ with $r = 0.69$ for the pooled data. Stroke volume correlated less closely with duration of systole than with duration of ejection. The regression of duration of systole and stroke volume was also examined separately for each heart rate in each patient. Fig. 5 shows plots of duration of systole against stroke volume at three heart rates in patient C. S. Table III B lists the regression equations for all ten heart rates from the same patient. At each heart rate, duration of systole changed much less than duration of ejection for a given change in stroke volume. The slope of the regression of duration of systole and stroke volume for each heart rate is about half that of the regression for the whole range of heart rates in this patient. The findings in the other subjects were similar.

The individual correlations of heart rate and duration of systole shown in Table IV B generally were better than the correlation of heart rate and duration of ejection (Table IV A). Duration of systole and heart rate were plotted and analyzed separately for beats grouped by stroke volume decades. Table V B lists the results of regression of duration of systole and heart rate for seven stroke volume decades from patient C. S. Table VI B shows the results of multiple regression analysis of duration of systole on stroke volume and heart rate. The standardized regression coefficients shown in Table VI B indicate that except in two patients heart rate accounted for more of the observed variance of duration of systole than did stroke volume.

Stroke volume varied inversely with pre-ejection period and demonstrated a mediocre correlation (Table VII). At any given stroke volume pre-ejection period also varied inversely with heart rate in every patient.

Good indivdual correlations were noted between stroke volume and pulse pressure (Table VII). The relationship was linear and its slope and intercept did not appear to be affected by heart rate (see Fig. 6). Table

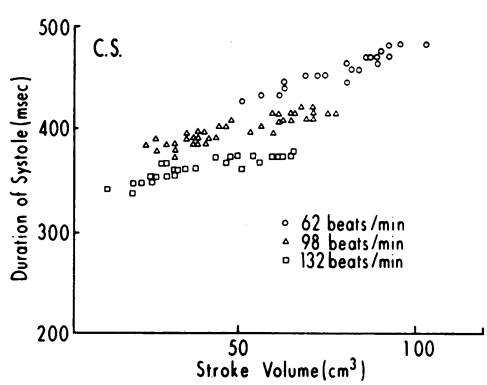

FIGURE 5 Relationship of stroke volume and duration of systole at three ventricular rates in patient C. S.

B. Duration of systole

Regression equation	Correlation coefficient, r			Standardized regression coefficients*	
	Stroke volume‡	Heart rate‡	Stroke volume and heart rate	Heart rate	Stroke volume
DS = 339.8 + 1.04 SV − 0.43 HR	0.91		0.95	−0.31	+0.76
DS = 405.6 + 0.45 SV − 0.72 HR		0.95	0.97	−0.73	+0.28
DS = 384.0 + 0.92 SV − 0.37 HR	0.88		0.89	−0.35	+0.56
DS = 454.3 + 0.94 SV − 0.98 HR		0.94	0.98	−0.64	+0.41
DS = 484.9 + 0.60 SV − 0.98 HR		0.87	0.92	−0.66	+0.37
DS = 369.6 + 0.46 SV − 0.59 HR		0.83	0.88	−0.64	+0.36
DS = 402.7 + 0.72 SV − 0.58 HR		0.78	0.86	−0.71	+0.36
DS = 325.8 + 0.38 SV − 0.32 HR		0.60	0.73	−0.50	+0.42
DS = 455.1 + 0.25 SV − 0.88 HR		0.84	0.87	−0.80	+0.24

VII (column 2) shows the regressions for pulse pressure and stroke volume for each subject.

Mean systolic flow correlated well with peak flow (Table VII) and the relationship appeared linear and independent of heart rate in every subject. The upper right panel of Fig. 2 shows the relationship between stroke volume and peak flow for all heart rates in patient C. S. The relationship is clearly curvilinear. However, when peak flow and stroke volume were plotted for each heart rate in each patient, it was seen that the relationship was linear and the correlations were very close. Table VIII lists the relationships of peak flow and stroke volume at selected heart rates in all subjects. In each subject the slope of the relationship increased with heart rate so that at faster rates a particular stroke volume was associated with a higher peak flow. This is illustrated by Fig. 7 which shows the relationship of peak flow and stroke volume for two heart rates from patient C. S.

The usefulness of duration of ejection, heart rate, and

TABLE VII

Relationships between Various Hemodynamic Parameters

Patient	Stroke volume vs. pulse pressure		Pre-ejection period vs. stroke volume	Peak flow vs. duration of ejection	Peak flow vs. mean systolic flow
	Regression equation	Correlation coefficient, r			
			r	r	r
H. B.	PP = 0.655 SV + 10.02 ±5.86	0.89	0.71	0.88	0.98
H. W.	PP = 0.456 SV − 2.39 ±2.65	0.95	0.54	0.89	0.94
A. S.	PP = 0.904 SV + 3.70 ±5.30	0.94	0.76	0.93	0.92
C. S.	PP = 0.503 SV − 0.18 ±2.88	0.96	0.61	0.91	0.96
N. T.	PP = 0.870 SV + 3.65 ±4.35	0.97	0.82	0.86	0.97
D. L.	PP = 0.427 SV + 3.78 ±2.98	0.89	0.42	0.89	0.96
A. H.	PP = 1.232 SV + 0.49 ±3.07	0.94	0.91	0.84	0.97
J. S.	PP = 1.034 SV + 3.88 ±7.80	0.82	0.78	0.87	0.97
E. A.	PP = 0.535 SV + 5.02 ±2.75	0.92	0.76	0.92	0.97

PP refers to the pulse pressure in mm Hg.

TABLE VIII

Correlation of Peak Flow and Stroke Volume* at Different Heart Rates*

Patient	Heart rate	Regression equation	Correlation coefficient, r
	beats/min		
H. B.	97	PF = 218.3 + 2.89 SV ±14.1	0.96
	109	PF = 150.1 + 3.68 SV ±14.6	0.97
	139	PF = 135.2 + 4.56 SV ±11.9	0.99
H. W.	59	PF = 232.7 + 2.94 SV ±8.5	0.90
	111	PF = 182.1 + 4.45 SV ±11.1	0.98
	146	PF = 113.2 + 6.04 SV ±20.0	0.97
A. S.	34	PF = 153.5 + 4.46 SV ±22.3	0.86
	52	PF = 150.6 + 4.28 SV ±9.9	0.93
	109	PF = 100.1 + 6.06 SV ±9.4	0.96
C. S.	62	PF = 239.2 + 2.51 SV ±11.1	0.95
	98	PF = 155.7 + 4.18 SV ±14.7	0.98
	120	PF = 108.3 + 5.46 SV ±9.3	0.99
N. T.	78	PF = 76.3 + 4.38 SV ±10.0	0.98
	104	PF = 74.1 + 5.26 SV ±8.8	0.99
	117	PF = 65.4 + 5.81 SV ±11.6	0.99
D. L.	100	PF = 103.0 + 6.63 SV ±16.6	0.97
	128	PF = 99.5 + 7.07 SV ±28.1	0.95
	146	PF = 58.9 + 8.15 SV ±18.4	0.98
A. H.	118	PF = 81.0 + 4.81 SV ±12.9	0.93
	133	PF = 73.9 + 5.59 SV ±7.2	0.98
	158	PF = 69.8 + 6.18 SV ±8.2	0.98
J. S.	111	PF = 82.4 + 6.83 SV ±20.1	0.96
	125	PF = 69.9 + 7.43 SV ±13.3	0.99
	143	PF = 54.4 + 8.83 SV ±13.3	0.98
E. A.	100	PF = 76.0 + 6.62 SV ±15.8	0.99
	122	PF = 73.0 + 7.58 SV ±18.8	0.98

* Peak flow (PF) appears in cubic centimeters per sec and stroke volume (SV) appears in cubic centimeters.

pulse pressure in the prediction of stroke volume were examined by multiple regression analysis of all the data from the nine patients. Duration of ejection alone gave the equation $SV = 0.434\ DE - 40.9$ (SEE ±7.2 cm³) with a correlation coefficient of $r = 0.94$. Duration of ejection and heart rate gave the equation $SV = 0.501\ DE + 0.130\ HR - 67.2$ (SEE ±7.2 cm³) and a very slightly improved correlation coefficient of $r = 0.95$. Adding pulse pressure (PP) to duration of ejection and heart rate gave the equation $SV = 0.496\ DE + 0.130\ HR + 0.020\ PP - 66.9$ (SEE ±7.5 cm³) with an unchanged correlation coefficient of $r = 0.95$.

The product of pulse pressure in mm Hg and duration of ejection in seconds was examined as an index of stroke volume. Table IX shows a good correlation in most patients but wide variation in the slopes and intercepts of the relationship from patient to patient. The correlation of the product of pulse pressure and duration of ejection with stroke volume was, therefore, poor when data from all nine patients were pooled.

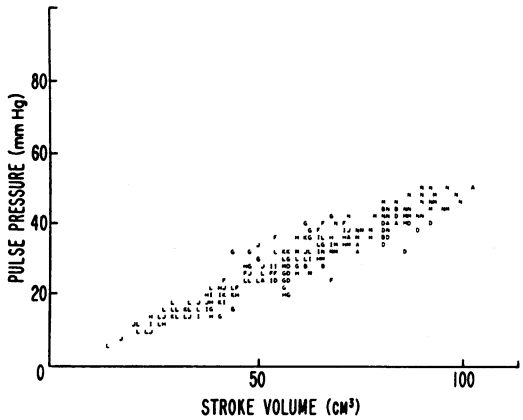

FIGURE 6 Plot of pulse pressure and stroke volume over the whole range of ventricular rates in patient C. S. demonstrating a linear relationship. Each letter represents a different period of recording and in most cases a separate ventricular rate.

DISCUSSION

The wide range of stroke outputs observed at a given ventricular rate in these patients is due primarily to variations in ventricular filling. Differences in the timing of atrial systole relative to ventricular contraction probably accounted for the bulk of these changes. In addition, small variations in ventricular filling undoubtedly resulted from the effects of respiration. Since the ventricular rate was regular at each rate studied, the inotropic effect produced by changing the heart rate was avoided (5). It is possible that respiratory variations in vagal efferent activity may have caused a slight rhythmic alteration in ventricular contractility (6). Nevertheless,

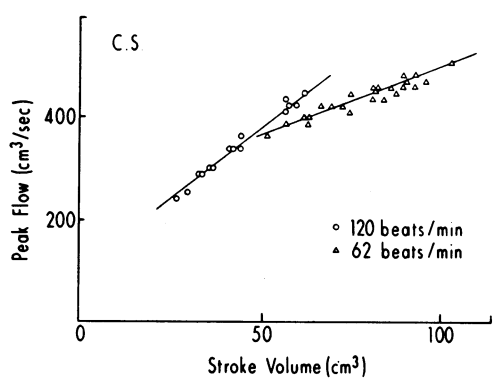

FIGURE 7 Relationship of peak flow and stroke volume at two ventricular rates in patient C. S. The lines represent the regressions shown in Table VIII, lines 10 and 12.

TABLE IX

*Multiple Correlation of the Product of Pulse Pressure and Duration of Ejection with Stroke Volume**

Patient	Regression equation		Correlation coefficient, r
H. B.	SV = 4.58 x + 10.5	±5.9 cm³	0.94
H. W.	SV = 6.29 x + 24.6	±5.3 cm³	0.95
A. S.	SV = 2.83 x + 18.4	±5.2 cm³	0.95
C. S.	SV = 5.36 x + 20.0	±5.3 cm³	0.96
N. T.	SV = 4.06 x + 5.9	±5.0 cm³	0.96
D. L.	SV = 8.16 x + 11.4	±5.0 cm³	0.93
A. H.	SV = 3.35 x + 6.1	±2.4 cm³	0.93
J. S.	SV = 3.65 x + 8.4	±5.6 cm³	0.86
E. A.	SV = 7.96 x + 2.2	±4.1 cm³	0.95
All	SV = 3.92 x + 19.95	±14.2 cm³	0.77

* x is the product of pulse pressure in mm Hg and duration of ejection in seconds.

it seems reasonable to assume that alterations in ventricular filling and not changes in contractility accounted for most of the variation in stroke output observed at each specific heart rate. Alterations in rate may produce changes in the contractile state of the heart. However, in this group of patients the relative contribution of both stroke volume and heart rate to the duration of the phases of systole have been assessed during as constant an inotropic state as is possible to achieve in man.

Experimental work, using isolated supported heart (7) and right heart bypass preparations (8), has shown that when heart rate and blood pressure are maintained at a constant level, the duration of ejection varies directly with stroke volume, whereas the duration of total systole is relatively independent of the stroke volume. Similarly, when blood pressure and stroke volume are maintained constant both the duration of ejection and total systole are inversely related to heart rate. Remington, Hamilton, and Ahlquist have shown similar relationships in pooled single measurements from intact dogs under a wide variety of conditions (9). In man, attention has been predominantly directed at the relationship between heart rate and the phases of systole both in groups and in individual subjects. Studies in single subjects have involved the use of exercise (10–17), drugs (11, 18, 19), or other maneuvers (15, 20, 21), to alter heart rate. The resulting changes in the duration of both ejection and systole depend not only on heart rate, but also upon changes in stroke volume and in the inotropic background produced by the interventions.

Recently, Greenfield, Harley, Thompson, and Wallace examined the beat to beat relationship of stroke volume and duration of ejection by means of the pressure gradient technique in patients with atrial fibrillation in whom the inotropic milieu was assumed constant (22). Random variation in cycle length produced variation in stroke volume which correlated very closely with duration of ejection both in individual patients and in the whole group. However, since changes in stroke volume in atrial fibrillation are intimately related to the changes in cycle length, the relative effects of changes in cycle length (heart rate) and stroke volume on duration of ejection could not be examined independently. The present study defines the extent to which heart rate and stroke volume are related to the duration of ejection. Stroke volume appears to be primarily related to the duration of ejection, although a lesser but independent effect of heart rate is clearly present.

The slopes of the regression equations relating heart rate and duration of ejection over the whole range of stroke volumes in each patient (Table IV) are approximately the same as that found by several investigators (17, 23), but less than that observed by others (20, 24, 25). Differences in the slope of this relationship noted by these workers can be explained by the extent to which the interventions used to alter heart rate changed stroke volume as well. Although experimental work in the dog (7, 8) has indicated that stroke volume was a major determinant of the duration of ejection, several authors have examined the multiple correlation of duration of ejection, stroke volume, and heart rate in man with incongruous results. From such studies it has been concluded that stroke volume is of no importance in determining duration of ejection (16), that stroke volume has a significant but relatively minor effect (13), and that stroke volume is an important determinant of duration of ejection (20). The reasons for these conflicting results apparently stem from the use of pooled data from many individuals and the use of interventions which alter both stroke volume and heart rate simultaneously. In this present study holding the rate constant by ventricular pacing and the ability to measure beat to beat alterations in aortic blood flow permitted these difficulties to be overcome for the first time in man.

It is of interest that in general, the relationship of stroke volume and duration of ejection appears to be linear both over a wide range of heart rates and at a constant heart rate. This finding contrasts with the exponential relationship of stroke volume and duration of ejection noted in patients with atrial fibrillation in our laboratory (22). In patients with atrial fibrillation it appears that rapid fluctuations in cycle length may induce beat to beat changes, not only in ventricular filling, but also in ventricular contractility.

As in previous studies, the duration of total systole was found to vary inversely with heart rate (8). The relationship held in a given patient both over a wide range of stroke volumes and at a fixed stroke volume. Heart rate correlated more closely with duration of sys-

tole than with the duration of ejection, both over the whole range of stroke volumes for each patient and within each stroke volume decade. The regression equation relating duration of systole to heart rate for the data from all nine patients is similar to the one obtained from pooled individual measurements in 205 healthy subjects by Krayenbühl, Rubli, Gander, and Hegglin (26). However, the slopes of the regression equations for our individual patients were smaller than those calculated for the pooled data. In each subject the slope of the relation between the duration of systole and heart rate for a fixed stroke volume decade was even less than for the data at different stroke volumes. These differences in slope were due to the effect of stroke volume, which, although it correlates less closely with the duration of systole than with the duration of ejection, varies directly with the duration of systole over the whole range of heart rates in each patient and at fixed heart rates. Thus, one cannot reasonably use pooled data to predict the relationship which exists when the effect of stroke volume is removed.

The influence of stroke volume on duration of systole at fixed heart rates has been demonstrated in the anesthetized dog (27), and has been suspected in man from observations on the changes in duration of systole with posture (15, 21). However, the same criticisms of previous studies of the duration of ejection apply whenever duration of systole is changed by interventions which change stroke volume and heart rate simultaneously. The response of duration of systole to digitalis, catecholamines, exercise, and other interventions can only be interpreted in terms of the changes in both heart rate and stroke volume which they produce. Thus, the value of the duration of systole over a range of heart rates and stroke volumes must be known before one can conclude that changes in duration of systole reflect a direct inotropic effect (28, 29). It is possible that the relative independence of duration of systole from beat to beat changes in stroke volume observed in patients with atrial fibrillation was due to the particular relationship between stroke volume and cycle length, which existed in the patients studied (22). Shortening of the duration of systole in cardiac failure and other conditions may merely represent reduced stroke volume rather than abnormal contractility (26, 30, 31).

The behavior of the pre-ejection period can be deduced from the relationships of duration of systole and duration of ejection to stroke volume and heart rate. Pre-ejection period varied inversely with stroke volume and heart rate and may, therefore, remain constant in the presence of interventions which change heart rate and stroke volume in opposite directions. It is clear that this period can only be regarded as an index of contractility in terms of the relation to stroke volume and heart rate for any particular beat. Thus, in the past, the explanation of the effect of exercise and drugs on pre-ejection period has met with difficulty (11, 12).

Although a close linear relationship was found between the stroke volume and the pulse pressure for each subject in this study, the over-all correlation for the group was poor due to variations among individuals. Juchems reported an almost complete lack of correlation between single measurements of pulse pressure and stroke volume in 1000 subjects (32). In our patients, an excellent correlation was noted between the duration of ejection and the stroke volume both for each individual subject and for the entire group. Previous investigators have attempted to derive estimates of stroke volume from either the pulse pressure or from calculations based on the pressure pulse and the subintervals of systole (33). At the present time, there is an urgent need for a technique which can rapidly yield a continuous index of stroke volume. This would be especially relevant to the monitoring of acutely ill patients. Since stroke volume did vary widely in our patients, it would seem that both the pulse pressure and the duration of ejection might provide a reasonable index of the stroke volume for monitoring purposes. However, it must be remembered that the data obtained from our patients were recorded when both the systemic vascular resistance and inotropic cardiac state were relatively constant. Thus, the excellent correlations are representative of an ideal situation. In a patient undergoing significant changes in either vascular resistance and/or myocardial contractility, such as a patient with an acute myocardial infarction, these indices will probably not reflect true changes in stroke volume and must be used with caution. The product of the pulse pressure and the duration of ejection was also shown to give a reasonably good correlation with stroke volume for each individual patient in our study. Obviously, this index of stroke volume will have the same limitations described above. However, at the present time, in our hands, this computation appears to provide a useful index for estimating stroke volume. We feel that it is sufficiently accurate to warrant further evaluation in the monitoring of acutely ill patients.

ACKNOWLEDGMENTS

The authors are deeply indebted to Mr. Philip McHale for his help with the data analysis; to Miss Judith C. Rambert, Mrs. Kathleen Smith, Miss Della Holder, and Miss Debbie Hilliard for their invaluable technical assistance; to Smokey Walker who proved a continuing source of encouragement; and to the Medical Illustration Service of the Durham Veterans Administration Hospital. Mr. Charles W. Ledford of the Hewlett-Packard Company also rendered valuable support.

The research upon which this publication is based was performed pursuant to Research Grant HE09711 and by Contract PH-43-67-1440 from the National Institute of Health,

Public Health Service, Department of Health, Education, and Welfare.

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