Influence of Digitalization on the Contribution of Atrial Systole to the Cardiac Dynamics at a Fixed Ventricular Rate

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The hemodynamic consequences of acute digitalization in man have been reported in a few studies with controversial results. It has been stated that digitalis has little or no effect on the cardiovascular events in the absence of manifestations of heart failure and while it significantly improves cardiac function in the failing heart.

This paper describes the effect of acute digitalization on the cardiovascular dynamics in patients with complete heart block with a fixed ventricular rate and the effect of digitalization on the contribution of atrial systole to ventricular filling at a fixed ventricular rate.

Material and Methods

Six patients with complete atrioventricular block resulting from coronary disease were studied. This diagnosis was established by the presence of a history of myocardial infarction in two cases. In the remaining four cases this diagnosis was suspected on the basis of onset of heart block above age 60 and by the absence of any other etiologic factor that could explain the presence of heart block. The average age of the patients studied was 70.3 years. All patients had the wires of a permanent cardiac pacemaker (Charlack-Greatbatch fixed rate) implanted in the free wall of the left ventricle for treatment of heart block. The pacemaker rate was fixed within the range of 70 to 75 impulses per minute. The studies were performed 3 to 12 months after operation and at this time the patients had no major manifestations of heart failure although mild dyspnea on exertion was present in two cases.

The cardiac output was determined with the indicator-dilution technic with Indocyanine green (Cardiogreen) as an indicator. Details of this technic have been described in a previous report. Injection of the indicator in an amount of 6.25 mg. was made into the left medial cubital vein with sampling from the right brachial artery. A Gilford cuvette densitometer (Model 103 IR) was used to detect the injected dye. The output of the densitometer was coupled to the input of a dye-dilution computer (Model 130), and the area under the curve was obtained by this means.

The heart rate was measured from lead II of the electrocardiogram simultaneously recorded with the dye curves. Arterial pressures were recorded with a P23Db Statham strain-gage. Mean pressures were obtained by electronic filtering. First derivative of the brachial artery pressure was obtained by electronic means. Peripheral resistance, average ventricular power, and stroke power were calculated from previously described formulas. The tension-time index was calculated from Sarnoff's formula.

Measurements of the ejection time were obtained from the indirect carotid tracings taken at a fast paper speed of 200 mm. per second with 20 millisecond (msec.) time lines. Mechanical systole was calculated from a medium frequency (40 to 200 cycles per second) phonocardiogram recorded at the mitral area with a high impedance Cambridge crystal microphone in held expiration. This interval was measured from the beginning of the first vibration of the first heart sound to the beginning of the aortic component of the second heart sound. Isometric contraction time was derived by subtracting the mechanical systole (M1-A2) from the ejection.

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*C. Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.
†Gilford Instruments, Oberlin, Ohio.
‡Sanborn Company, Waltham, Massachusetts.
time. The time interval from the beginning of the first sound to the beginning of the upstroke of the carotid tracing was also measured. The time interval from the beginning of the QRS complex of the electrocardiogram to the beginning of the upstroke of the carotid tracing was measured and designated Q-U interval. All these measurements were obtained immediately after the recording of arterial pressures and dye curves. A minimum of 10 consecutive cardiac cycles was obtained for each time interval during the study. The time relationship of the P wave to the following QRS complex was measured ("P-R interval") and correlated with the other data. For the purpose of simplification the measurements were analyzed for values of the "P-R interval" as follows: P occurring during ventricular systole (PS), from 1 to 100, 101 to 200, 201 to 300, and 301 to 500 msec. Whenever more than one measurement was obtained for one of the above groups of the "P-R interval," the figures were averaged for that particular interval. The atrial rate was measured from the P-R interval of the electrocardiogram. Statistical analysis was made, and the p values were determined for the difference between values obtained before and after digitalization.

Three to five determinations of all measurements were taken at rest. The patient was then given an intravenous infusion of 1 mg. of strophanthin G (ouabain)* over 1 minute. Measurements were again taken at 1, 2, 4, 6, 10, 20, 30, 60, 90, and 120 minutes after digitalization.

The studies were performed with the patient in a supine position under local anesthesia without premedication.

### Results

#### Cardiac Index

The cardiac index at rest was below the limits of normal in four cases. The average figure for the entire group was 1.98 L./min./M.² (table 1). Digitalization resulted in a mild to moderate increase in this factor in all cases. This increase was evident in the 1-minute determination with a maximal response (21-per cent increase) occurring between the twentieth and thirtieth minute after digitalization, at which time the cardiac index was 2.41 L./min./M.² (p < 0.001) (fig. 1).

Subsequent determinations showed a gradual decline of the cardiac index to the control level. Since the heart rate was fixed throughout the study, these changes occurred exclusively by an increase in the stroke volume.

#### Stroke Index

The average stroke index at rest was 27 ml./beat/M.². After digitalization there was a progressive increase in the stroke index, which reached 33 ml./beat/M.² (p < 0.001) 20 minutes after digitalization (22-per cent increase) (fig. 1).

#### Peripheral Resistance

The systemic resistance was 1,836 dynes sec./cm.⁵. There was a slight increase in this factor 2 minutes after digitalization. As the cardiac index rose and the mean pressure remained stable, the peripheral resistance decreased (20 per cent) to 1,526 dynes sec/cm.⁵ (p < 0.001), with a gradual return to the control values in the subsequent determinations (fig. 4).

#### Average Ventricular Power Index

The average ventricular power index progressively increased from a resting figure of 3.6 Kg. M./min./M.² to a maximum of 4.1 Kg. M./min./M.² (13-per cent increase) obtained 20 minutes after digitalization (fig. 4).

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*Eli Lilly Laboratories, Indianapolis, Indiana.
Table 1

Cardiovascular Hemodynamics before and after 1 mg. of Strophanthin G in Six Patients with Complete Heart Block

<table>
<thead>
<tr>
<th>Case, Sex</th>
<th>Event</th>
<th>Cl, L./min. / M.²</th>
<th>Sl, ml./beat / M.²</th>
<th>Bra, mm. Hg</th>
<th>Pr, mm. Hg Mean</th>
<th>P. Res., dynes sec. / cm.²</th>
<th>Vp, M./min. / M.²</th>
<th>Tti, mm. Hg/sec.</th>
<th>Sp, M./sec. / M.²</th>
<th>Ar, beats/min.</th>
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<td>40</td>
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<td>315</td>
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Influence of Atrial Systole on Cardiac Functions before and after Digitalization

Atrial and Ventricular Rate

The ventricular rate was fixed throughout the experiment in all cases (table 1). The rate of pacing ranged from 70 to 75, with an average rate of 72. The atrial rate averaged 75 per minute in the control figures. The administration of ouabain did not produce changes in either the atrial or the ventricular rate. One patient developed bigeminal rhythm 90 minutes after digitalization and 90-120-minute measurements were therefore not included in the study.

Brachial Artery Pressure

As described in a previous report,21 beat-to-beat variation in the values of the systemic pressure occurred in all cases. The higher values were recorded when the “P-R interval” was in the range of 80 to 300 msec. During this time interval not only the arterial pressures were high but the ejection time was prolonged as described below (fig. 2).

The first derivative of the brachial artery pressure, i.e., dp/dt, was measured in three cases and correlated with the “P-R interval”. For any given “P-R interval,” digitalization resulted in a higher dp/dt, as illustrated in figure 3.

The systolic, diastolic, and mean pressures rose slightly after digitalization with 5-, 7-, and 10-per cent increases, respectively (fig. 1). These values were not statistically significant, with p values greater than 0.05 for both systolic and mean pressures.

Tension Time Index

An analysis of this factor as a function of the “P-R interval” showed that the tension-time index was 2,053 mm. Hg sec./min. when the P wave occurred during the QRS-T complex and increased to a maximum of 2,430 mm. Hg sec./min. (18-per cent increase) when the P wave occurred during a “P-R interval” between 201 and 300 msec. Digitalization resulted in a uniform decrease of the tension-time index for all ranges of the “P-R interval” (fig. 5).
Stroke Power

The stroke power at rest was 184 Gm. M./sec./M.\(^2\) and increased to 236 Gm. M./sec./M.\(^2\) (28-per cent increase) 20 minutes after digitalization (\(p < 0.001\)) (fig. 4). An analysis of this value as a function of the

**Figure 2**

Brachial artery pressure showing the variation in the values of the systolic pressure and ejection time as a function of the “P-R interval.” Observe the lack of changes in the diastolic pressure. The values written under the area of the pressure curves represent the figures for the ejection time.

**Figure 3**

Peak derivative of the brachial artery pressure before and after digitalization as a function of the “P-R interval” in one case. Note a significant increase in these figures after digitalization.

**Figure 4**

Average values for peripheral resistance (Per. Res.), ventricular power (V.P.), tension time index (T.T.I.), and stroke power (S.P.) in six patients with complete heart block before and after administration of 1 mg. of strophanthin G. Note a decrease in the peripheral resistance with a rise in the ventricular power and stroke power after digitalization.

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Figure 5
Average tension time index (T.T.I.) in six patients with complete heart block before and after digitalization.

“P-R interval” revealed slightly higher figures when P waves occurred during the QRS-T complex as compared with the values obtained for the optimum “P-R interval.” Administration of ouabain increased the stroke power for all ranges of the “P-R interval” (fig. 6).

Ejection Time
The average ejection time showed its low-

Figure 6
Average stroke power (S.P.) in six patients with complete heart block before and after digitalization.

Figure 7
Ejection time measurements made in several cardiac cycles in one patient with heart block before and after digitalization. Note the increase in the ejection time when atrial systole occurs between 100-300 msec. Observe the effect of digitalization in decreasing the ejection time.

Figure 8
Average ejection time figures as a function of the “P-R interval” in six patients with complete heart block. Note the significant decrease after digitalization.
Table 2

Measurements of Ejection Time, Isometric Contraction Time and Q-U Interval before and after 1 mg. of Strophanthin G in Six Patients with Complete Heart Block

<table>
<thead>
<tr>
<th>Case</th>
<th>Event</th>
<th>P-S</th>
<th>1-100</th>
<th>ET, msec.</th>
<th>P-R Interval</th>
<th>101-200</th>
<th>201-300</th>
<th>301-500</th>
<th>P-S</th>
<th>1-100</th>
<th>ET, msec.</th>
<th>P-R Interval</th>
<th>101-200</th>
<th>201-300</th>
<th>301-500</th>
<th>P-S</th>
<th>1-100</th>
<th>Q-U Interval, msec.</th>
<th>P-R Interval</th>
<th>101-200</th>
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Key: P-S, P wave occurring during ventricular systole; ET, ejection time; msec., millisecond; IC, isometric contraction; Q-U, Q wave to the upstroke; C, control; m., minutes; A., after. Many other determinations were made after digitalization. However, for simplification, they were not used in this table.
est figure of 234 msec. when the P wave occurred during the QRS-T complex of the electrocardiogram (PS = P wave occurring during systole, figs. 6 and 7). Progressive increase in the “P-R interval” resulted in a significant increase in the ejection time to 277 msec. (18 per cent increase) with a maximal response obtained for the “P-R interval” between 100 and 300 msec. (table 2). Further prolongation of this interval from 300 to 500 msec. resulted in a decrease of the ejection time to 256 msec. It was also observed that short “P-R intervals” between 1 and 50 msec. showed figures for the ejection time, which were nearly equivalent to the ones observed for “P-R intervals” above 300 msec. Thus, the optimum contribution of atrial systole to ventricular filling is situated within a range of 50 per cent of the diastolic phase of the cardiac cycle. Its occurrence below or above this range contributed little to ventricular filling.

With these changes in ejection time there was also a 10- to 30-mm. Hg variation in the systolic arterial pressure with the highest figure obtained for both ejection time and pressure when the “P-R interval” was within the “optimum range” (fig. 11).

After digitalization there was a significant decrease in the ejection time which was uniformly present for all ranges of the “P-R interval” (figs. 8 and 9). After digitalization the ejection time did not increase proportionately during the optimum “P-R interval” as compared with the figures obtained prior to administration of ouabain.

In one case (P.L.) the P wave was inscribed during the QRS complex in all beats before and after digitalization. This gave us an opportunity to study the effect of digitalization on the ejection time at a fixed ventricular rate without the variations resulting from the P-QRS relationship. It was observed that the ejection time decreased progressively from a control figure of 226 msec. to a maximum of 202 msec. (11 per cent) observed 30 minutes after digitalization (fig. 10).
**Effect of digitalization on the isometric contraction time before and after digitalization in one case with complete heart block.**

**Mechanical Systole**

First sound-second sound interval. The changes in mechanical systole paralleled the changes observed in the ejection time (table 2).

**Isometric Contraction Time**

Significant changes occurred in calculated isometric contraction time. The isometric contraction time was 64 msec. when the P wave occurred during ventricular systole. With progressive increase in the “P-R interval” the isometric contraction time increased to a maximum of 80 msec. (25-per cent increase), which occurred for the “P-R interval” between 101 and 200 msec. Further increase in the “P-R interval” resulted in shortening of the isometric contraction time to 48 msec. The figures obtained for the “P-R interval” above 300 msec. were nearly identical to the ones obtained for the P wave occurring during ventricular systole.

Digitalization resulted in a uniform decrease in isometric contraction time (fig. 11). The contribution of atrial systole to the increase in isometric contraction time was also significantly reduced after digitalization.

The time interval between the first sound of the phonocardiogram and the beginning of the upstroke of the carotid tracing were measured. The changes observed paralleled the ones obtained for the isometric contraction time. Again, after digitalization the contribution of atrial systole to prolongation of this interval was significantly diminished.

**Q-U Interval**

This time interval averaged 202 msec. when the P wave was inscribed during ventricular systole. Progressive increase in the “P-R interval” resulted in a decrease of the Q-U interval with a maximal response obtained for the “P-R interval” between 100 and 300 msec. Digitalization decreased this time interval for any given “P-R interval” (fig. 9).

**Discussion**

Previous observations have indicated that digitalization produces a significant increase in the cardiac output and stroke volume in patients with heart failure and little or no change in these factors in non-failing hearts. However, concomitantly with the increase in the cardiac output and the stroke volume there is a slowing of the heart rate. Thus, the influence of digitalis on the stroke volume has not been fully resolved. Our observations indicate that acute digitalization does indeed increase stroke volume and cardiac output independently of the ventricular rate since this factor was maintained constant throughout the study by a permanent pacemaker. This effect may be accomplished even in the absence of overt manifestations of heart failure. It is recognized that the patients studied do not have normal hearts and the possibility of a mild degree of heart failure cannot be excluded with certainty.

The exact mechanism of action of digitalis is still the subject of considerable controversy. Direct measurements of myocardial contractile force in the nonfailing human heart have been made by Braunwald et al. using the strain-gage arch. They have shown that digitalization resulted in an increase in the myocardial contractile force and suggested that its effect on human hearts is somewhat identical to the ones obtained in the intact dog or in isolated heart muscle preparations.

Our findings indicate that digitalis improves...
CONTRIBUTION OF ATRIAL SYSTOLE

Circulation, Volume XXXII, July 1965

cardiac output in chronically stressed hearts with a fixed ventricular rate by means of an exclusive increase in the stroke volume.

The effect of digitalis on the peripheral circulation producing vasoconstriction and increased resistance has been documented by Dock and Tainter and Katz et al. A direct pressor effect of this drug in dogs has also been known to occur. Our studies demonstrate that in patients with a fixed ventricular rate there is a slight decrease (7 per cent) in mean arterial pressure. However, the significant decrease (20 per cent) in the peripheral resistance observed in our study is not seen in patients with normal sinus mechanism. The reason for this type of response is not known but the only difference between our patients and the patients described in these reports is the lack of synchronization between atrial and ventricular systole.

Digitalization resulted in an increase in the stroke volume despite an over-all decrease in the left ventricular ejection time and in the mechanical systole. A similar type of response of the stroke volume is also seen during exercise and during infusion of isoproterenol in patients with heart block. Since the atrial and ventricular rates were constant throughout the experiment, the decrease in ejection time and mechanical systole must have resulted from a direct effect of this drug on the myocardium with a consequent increase in the mean rate of flow.

Wiggers and Stimson, Cotten and Bay, and Weissler et al. found that digitalis shortens the period of isometric contraction in conditions in which the atrial and ventricular rates were synchronized and allowed to vary. Our studies substantiate these observations and extend them to conditions in which the ventricular rate is fixed with atrial systole occurring at various time intervals during the cardiac cycle.

The contribution of atrial systole to ventricular filling has been documented by several previous studies. Patients with complete heart block and fixed ventricular rates provide an ideal experimental model to study the contribution of atrial systole to ventricular filling by virtue of a varying time relationship of the P wave to the QRS complex.

Atrial systole contributes to ventricular filling to a significant degree as manifested by an increase in the ejection time when atrial systole occurred between 100 and 300 msec. prior to the following QRS complex. This range is critical since P waves occurring beyond 300 msec. and at less than 100 msec. to the following QRS complex do not significantly influence either ejection time or isometric contraction time. It seems that atrial systole is of significant benefit to ventricular filling in the chronically stressed heart; once cardiac function is improved, however, by the administration of digitalis then the contribution of atrial systole becomes relatively of less significance. As demonstrated by Linden and Mitchell in dogs with heart block, atrial contraction produced only a small rise in the ventricular diastolic pressure with a great increase in myocardial segment length.

Thus it is suggested that digitalis has an inotropic effect on the heart, which is characterized by an increase in the cardiac output, stroke volume, and stroke power with a decrease in ejection time and isometric contraction time. Its effect on the peripheral circulation producing vasodilatation and decreased systemic resistance is different from that observed in patients with normal sinus mechanism and fixed “P-R interval.”

Summary and Conclusions

The cardiovascular hemodynamic effects of 1 mg. of g-strophanthin were studied in six patients with complete heart block and fixed ventricular rate. Digitalization resulted in 21-, 22-, 13-, and 28-per cent increases in the cardiac index, stroke index, ventricular power, and stroke power, respectively, in the absence of any change in the ventricular or atrial rates. The arterial pressure did not change significantly after digitalization.

Variations in the “P-R interval” of the electrocardiogram resulted in significant changes in the ejection time, stroke power, and tension-time index. For the “optimum P-R interval” between 100 and 300 msec. there was an increase in the ejection time. Very short
“P-R intervals” and P waves occurring during ventricular systole resulted in little or no change in the ejection time. Digitalization diminished the contribution of atrial systole to ventricular filling.

Atrial systole occurring during the “optimum P-R interval” prolonged isometric contraction time. This increase was diminished or abolished after digitalization.

It is concluded that digitalis exerts its effect by a primary inotropic action, thereby increasing cardiac output, stroke volume, and stroke power while decreasing ejection time and isometric contraction time independently of changes in ventricular or atrial rates. Its possible effect on the peripheral circulation producing vasodilatation is also suggested on the basis of a decrease in the peripheral resistance after digitalization in the absence of any significant changes in the systemic pressure.

Acknowledgment

We are grateful to Mrs. Mary Vensel, Miss Marilyn Hanna, Miss Shirley Cardwell and Miss Ann Wall for their technical assistance.

References


CONTRIBUTION OF ATRIAL SYSTOLE

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Influence of Digitalization on the Contribution of Atrial Systole to the Cardiac Dynamics at a Fixed Ventricular Rate
ALBERTO BENCHIMOL, HUGO A. PALMERO, MARVIN S. LIGGETT and E. GREY DIMOND

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