Changes in Diastolic Time with Various Pharmacologic Agents

Implication for Myocardial Perfusion

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SUMMARY Diastolic time (DT) is calculated as the cycle length (RR) minus electromechanical systole (QS). The ratio of DT (RR-QS) to RR internal times 100, or the percent diastole (%D), varies nonlinearly with heart rate (HR), increasing rapidly with decreasing HR. The effect of commonly used cardioactive agents on %D was studied in five groups of normal subjects.

In group 1 (n = 12), propranolol (160 mg daily) increased %D from 55.9 ± 1.7 to 64.7 ± 1.3 (p < 0.001) by slowing HR. In group 2 (n = 12), dobutamine (2.5 μg/kg/min) increased %D from 56.4 ± 1.4 to 61.8 ± 1.3 (p < 0.005) by shortening the QS. In group 3 (n = 10), Cedilanid-D (1.6 mg i.v.) increased %D from 55.5 ± 1 to 63.2 ± 0.7 (p < 0.001), both by slowing the HR and shortening the QS. In group 4 (n = 12), isoproterenol (2 μg/min) increased HR and shortened the QS significantly. The net result was a significant reduction of %D from 56.1 ± 1.4 to 53.5 ± 1.1, (p < 0.05). In group 5 (n = 15), a 100-mg bolus of i.v. lidocaine did not have a significant effect on %D.

This study indicates that cardiovascular drugs may have significant effects on the relative duration of diastole either by affecting HR or the duration of systole. This may have clinical implications for patients with coronary artery disease and patients with left ventricular hypertrophy, since in both cases coronary flow is mostly diastolic.

DIASTOLIC TIME can be calculated as the cardiac cycle (RR) minus electromechanical systole (QS). It has a curvilinear relationship with heart rate (HR), increasing rapidly as rates fall below 75 beats/min. Cardioactive drugs may affect diastolic time by altering HR, QS or both. Subendocardial perfusion and perfusion distal to a significant obstruction in patients with coronary artery disease is nearly all diastolic. As such, it is related not only to diastolic perfusion pressure and microcirculatory tone, but also to the diastolic time.1-10

While the effect of cardioactive drugs on systolic time intervals (STIs) has been studied,11,14 the effect of these agents on diastole has not been emphasized. In this study we investigated the effect of commonly used cardioactive drugs on diastolic time in normal subjects.

Material and Methods

The total QS interval for the normal population is linearly related to HR by the following regression equations:18,16

\[ QS_2 = 546 - 2.1 \text{ HR (males) } \]  
\[ QS_2 = 549 - 2.0 \text{ HR (females) } \]  

Since the time of a complete RR interval is the reciprocal of HR,

\[ RR (\text{msec}) = \frac{60,000}{HR} (\text{msec/min}) \]  

both the RR and the systolic period (QS2) may be expressed as a function of HR (fig. 1A). The difference between these two equations (RR and QS2) thus represents the diastolic time period for a given HR. The diastolic period so calculated begins with the aortic valve closure and terminates with the beginning of the QRS. By using either the ratio of the diastolic time to the systolic time period, or the ratio of the diastolic time period to the cardiac cycle (RR), these results can be expressed in a single equation as a function of HR. Figure 1B is a plot of the percent diastole vs HR and was derived simply by dividing the diastolic period (diastole = RR - QS2) by the cardiac cycle (RR) and by multiplying by 100.

Incorporating equations 1, 2, and 3,

\[ \% \text{Diastole} = 100 - \frac{546}{600} \text{ HR} + \frac{2.1}{600} (\text{HR})^2 \]  
\[ = 100 - \frac{549}{600} \text{ HR} + \frac{2.0}{600} (\text{HR})^2 \]  

The above equations are in the form of a polynomial of the second order. Data expressed as percent diastole may be analyzed by performing a general linear test on values fitted to the second-order curve. Significant differences may then be determined between corresponding groups.

Figure 1B shows that percent diastole is strongly influenced by HR. Due to the inverse relationship between RR length and HR (fig. 1A), small changes in HR produce significant changes in the diastolic period at lower HRs. By using the percent diastole format, individual systolic, diastolic and HR data can be ex-
pressed as a single relationship, and can be obtained from the nomogram shown in figure 2.

Physiologic and/or pathological states and pharmacologic agents can affect the percent diastole by two means. One is by direct effects on HR, while the other involves a fundamental change in the HR—percent diastole relationship. Changes in HR alone produce movement along the curve. Shortening of $Q_2$ causes an upward shift of the curve, while prolongation of $Q_2$ results in a downward shift. A combination of both of these factors produces both shifting and movement along the curve.

Sixty-six normal subjects, all males, ages 18–29 years (mean 25 years) and weighing 60–89 kg (mean 71 kg) were studied. Serial STIs were measured before and after administering various pharmacologic agents. The subjects were divided as follows:

**Group 1**

Twelve subjects took propranolol orally (160 mg daily) for 2 days in four divided doses. The STIs were obtained as a control three times and then every hour for 4 hours after the last dose of propranolol. The mean values from the three control measurements were used for the analysis. After propranolol the values at the slowest HR were used.

**Group 2**

In 12 subjects STIs were obtained three times before and twice after 20 minutes of a constant intravenous infusion of dobutamine at 2.5 $\mu$g/kg/min. The mean values before and after dobutamine were used for the analysis.

**Group 3**

In 10 subjects STIs were obtained three times as a control and at 10, 20, 40, 60 and 160 minutes after Cedilanid-D (1.6 mg) was given i.v. The mean values from the three control measurements were used for the analysis. After digitalis the values with the shortest $Q_2$ were used.

**Group 4**

In 12 subjects STIs were obtained before and after infusion of isoproterenol at 2 $\mu$g/min for 10 minutes.

**Group 5**

In 15 subjects STIs were obtained three times as a control and at 1, 3, 5, 7, 10, 15 and 30 minutes after a
100-mg bolus of lidocaine i.v. The mean values from the three control measurements and values 3 minutes after lidocaine were used for the analysis, since the peak effect of lidocaine on the STIs occurs at that time.12

STIs were measured as described previously from our laboratory.15, 16 Total QS2 was measured from the onset of ventricular depolarization to the first high-frequency vibration of the aortic component of the second heart sound. The total diastolic period was calculated by subtracting the QS2 from the RR interval.

Blood pressure was measured by sphygmomanometry each time with STI measurements.

Statistical analysis to determine the differences in HR and percent diastole between control and drug administration was performed by analysis of variance tests. Data in each case were fitted to a second-order polynomial of the form of equations 4 and 5 by the least-squares method. Differences between curves fitted to control and drug-administered subjects were determined by a general linear test based on direct comparisons of corresponding coefficients.17 A p value < 0.05 was considered significant.

Results

The coefficients of all our control measurements were not significantly different from the theoretical values.

The effect of pharmacologic agents on percent diastole is shown in figure 3. Propranolol significantly increased percent diastole from 55.9 ± 1.7 (SEM) to 64.7 ± 1.3 (p < 0.001), almost totally on the basis of the effect of the drug on HR (control 67.1 ± 3.3, propranolol 48.4 ± 2.2 beats/min, p < 0.001). There was no significant difference between regression coefficients relating HR and percent diastole before and after propranolol.

Dobutamine increased percent diastole from 56.4 ± 1.4 to 61.8 ± 1.3 (p < 0.005) without significantly altering the HR (65.6 ± 2.7 vs 61.6 ± 2.4). The increase in diastole was due to a shortening of the QS2. Thus, there was an upward shift in the regression relating HR and percent diastole after dobutamine administration (p < 0.005).

Cedilanid-D increased percent diastole from 55.5 ± 1 to 63.2 ± 0.7 (p < 0.001). There was also a significant difference (p < 0.05) between regression lines, again due to shortening of the QS2 (p < 0.05). Thus, change in percent diastole was the result of a combined effect of reduced HR and an upward shift of the curve.

Isoproterenol significantly shortened the percent diastole (56.1 ± 1.4 to 53.5 ± 1.1, p < 0.05). However, at any level of HR systole was also shortened, so diastole was correspondingly lengthened, resulting in an upward shift of the curve relating HR and percent diastole. The net result was less shortening of percent diastole than might have been expected with increased HR alone. There was no significant difference between percent diastole, HR or regression lines before and after lidocaine.

The duration of the QRS complexes did not change in any of the subjects throughout the study. Blood pressure was unchanged with propranolol, dobutamine, Cedilanid-D and/or lidocaine. Isoproterenol increased systolic blood pressure (122 ± 5 to 146 ± 5 mm Hg, p < 0.001) and decreased diastolic pressure (74 ± 2 to 59 ± 3 mm Hg, p < 0.001).

Discussion

Two factors determine the duration of the diastolic period: the HR and QS2. A decrease in HR and/or shortening in QS2 will result in a prolongation of total diastolic period and vice-versa. Due to the nonlinear relationship between HR and total diastolic period, small changes in HR can produce significant changes in diastolic period.

In our experiments, the total diastolic period was calculated from the RR interval by subtracting the QS2. Therefore, the electromechanical delay was included in the QS2. This period is very short (< 35 msec) in the absence of left bundle branch block,16 and nearly constant both before and after drug administration. The error in calculation of percent diastole due to exclusion of the electromechanical delay, although small, would cause an underestimation of the percent diastole and would be more pronounced at higher HRs.

The greatest proportion of coronary blood flow in normal humans occurs in diastole. Subendocardial flow is apparently totally diastolic, and this is especially pronounced when left ventricular hypertrophy is present.1-10, 18-22 In patients with severe obstructive coronary artery disease, systolic coronary flow may be lost, because the perfusion pressure distal to the obstructive lesions is less than the systolic ventricular wall pressure. The diastolic pressure distal to a significant obstruction is low, and probably does not change dramatically with aortic pressure changes.23-28 When perfusion pressure drops below a certain level, maximal vasodilation takes place. At this point coronary flow becomes dependent on the diastolic perfusion time as well as perfusion pressure.23, 26-28

It has been shown that the left ventricular intramyocardial stress during systole is greater in the subendocardial muscle layers of the heart. As a consequence of this distribution of stress, blood flow to the subendocardial layers occurs mostly during diastole, especially when hypertrophy is present. In contrast, the subepicardial muscle is perfused during diastole as well as during systole.29-33 When the subendocardial vessels lose their capacity to dilate (e.g., in hypoxia), flow to the endocardial layers depends on the diastolic blood pressure, the intramyocardial pressure and the duration of diastole. In 1972, Buckberg et al. found a good relationship between the ratio of subendocardial/subepicardial flow and the diastolic time (r = 0.73) in a wide variety of conditions in experimental animals.4

Propranolol, one of the most commonly used drugs in patients with coronary artery disease, significantly decreased HR, resulting in marked increase in percent diastole. It did not affect the relationship between the HR and the QS2.

Propranolol did not alter blood pressure as
measured by sphygomanometry. The effects on mean aortic diastolic pressure and left ventricular end-diastolic pressure were not measured, but are most likely minimal in normal subjects. The effect of propranolol on the diastolic perfusion pressure in ab-

normal subjects is more variable, depending on the initial arterial pressure and the left ventricular end-diastolic pressure. However, in the majority of instances the perfusion pressure is not dramatically altered by propranolol.\textsuperscript{34-38}

\textbf{FIGURE 3.} Effect of pharmacologic agents on percent diastole. A) Propranolol significantly increased percent diastole, primarily because of the effect on heart rate (HR). B) Dobutamine increased percent diastole without significantly altering the HR. The increase in percent diastole was due to the shortening of the duration of systole ($Q_S$). C) Cedilanid-D both shortened the duration of $Q_S$ and decreased the HR significantly. The net result was a marked increase in percent diastole. D) Isoproterenol increased the HR and shortened the $Q_S$ significantly. The net result was a small but significant decrease in percent diastole. E) There was no significant difference between percent diastole, HR or regression curve before and after lidocaine.

The $p$ value refers to significant difference in percent diastole.
Our data suggest that another mechanism for the beneficial effect of propranolol in angina pectoris may be an increase in diastolic myocardial perfusion time and hence, an increased myocardial blood flow. In experimental animals, propranolol has been shown to increase myocardial perfusion distal to stenotic coronary arteries; this had never been satisfactorily explained.\(^{34} \text{–} 40\) Due to the low resting sympathetic tone in our normal subjects, propranolol did not produce significant changes in QS, \(^{16}\) In many patients with coronary artery disease, however, adrenergic tone is increased and the QS is shorter than normal.\(^{13} \text{–} 41,43\) In these patients propranolol prolongs the QS.\(^{16}\) However, due to the curvilinear relationship between HR and diastolic time and to the fact that patients with coronary artery disease and increased adrenergic tone often have a faster HR than normal, the net effect of propranolol is still a marked increase in percent diastole (Boudoulas H, Lewis RP, Rittgers SE, Leier CV, Vasko JS: manuscript submitted for publication).

Dobutamine produced a significant shortening of the QS without a significant effect on HR; the net result was an increase in percent diastole. Dobutamine increases myocardial oxygen consumption because of its inotropic effect, but also may increase myocardial oxygen supply because of its effect on total diastolic period. Dobutamine has been shown to improve left ventricular performance in patients with acute myocardial infarction without increasing the extent of myocardial injury.\(^{44}\)

Digitalis, the most commonly used cardioactive drug in patients with heart failure, significantly decreased the HR and the QS.\(^{28}\) The net result was a marked increase in percent diastole. Digitalis has been previously shown to decrease infarct size in acute myocardial infarction with congestive heart failure. This effect was thought to be secondary to a decrease in left ventricular size, and therefore a decrease in myocardial oxygen consumption despite its accompanying inotropic effect. However, the effect of digitalis on diastolic time (and therefore increasing myocardial blood flow) may also be very important. Finally, a reduction in left ventricular end-diastolic pressure may also contribute to improved diastolic perfusion. Several recent studies suggest that digitalis increases regional myocardial flow after coronary artery occlusion in experimental animals without heart failure.\(^{36} \text{–} 44\)

Isoproterenol produced a significant increase in HR and a significant shortening of the QS.\(^{45} \text{–} 48\) The result was a decrease in percent diastole. Because of the marked decrease in the duration of the QS, the reduction of diastole was not as great as would have resulted from a change in HR alone. Aortic diastolic pressure was significantly reduced so that myocardial perfusion pressure was also undoubtedly reduced.

Lidocaine did not have any significant effect on percent diastole or blood pressure.

We conclude that pharmacologic agents can have a significant effect on diastolic time in normal subjects. In patients with heart disease or in experimental animals, these effects may be more striking because of relatively greater variations in HR. The effect of drugs on diastolic time, with consequent implications for coronary perfusion, should be considered along with the better known effects of such agents on myocardial oxygen consumption.

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