Continuous Determination of Beat-to-Beat Stroke Volume from Aortic Pressure Pulses in the Dog

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SUMMARY  Present methods for measurement of stroke volume from the aortic pressure pulse are not suitable for beat-to-beat determinations during non-steady state conditions because these methods assume that each systolic ejection is equal to the peripheral runoff during the same beat. We have tested a new method which allows determination of an aortic pressure-volume conversion factor over a wide range of pressures during transient changes in stroke volume and infusions of vasoactive drugs in 6 dogs with chronically implanted aortic electromagnetic flowmeters. Each aortic diastolic pressure decay is approximated by an exponential the time constant of which is used to calculate the pressure loss during systole due to blood flow into the periphery. The total increment in aortic pressure due to systolic ejection, if there were no flow from the aorta during systole, is calculated. The total systolic increment ($\Delta P_{SV}$) is assumed to describe the pressure-volume characteristics during systole and is related to stroke volume by a constant multiplier that is derived from the indicator-dilution measurements of cardiac output. The values for beat-to-beat variations that were determined by use of the aortic electromagnetic flowmeter and by this aortic pressure pulse method were found to be within the range of measurement errors of stroke volume determined from individual aortic electromagnetic flow pulses.

A FUNDAMENTAL tenet of most methods for estimation of stroke volume from aortic pressure pulses is that the left ventricular output into the arterial tree during systole is equal quantitatively to the blood flow into the periphery during the same cardiac cycle. This is equivalent to the assumption that at end-diastole the pressure falls to the same value as that observed at the beginning of the prior systole. Although such behavior may be observed during steady state conditions, it is unlikely during transient unsteady state conditions and results in a decrease in the accuracy of beat-by-beat calculations of stroke volume by these methods.

It generally is agreed that the increase in aortic pressure during the systolic ejection phase of the cardiac cycle is determined by (1) the stroke volume of that heart beat, (2) the pressure-volume characteristics of the arterial vessels, and (3) the drainage of blood out of these vessels into the periphery during systolic ejection. Of these three factors, the stroke volume can be determined directly by independent methods but the other two can be estimated only indirectly. However, beat-to-beat estimates of stroke volume from aortic pressure pulses require a knowledge of these two unknowns throughout each heart beat.

We describe here a method to circumvent this difficulty that is based on the two following assumptions: (1) that the decrement in aortic pressure, or more correctly the pressure increment which fails to occur, due to peripheral drainage of blood during any given systole can be estimated from the aortic pressure recorded throughout this systole and the time constant ($\tau$) of the decrease in aortic pressure during diastole; and (2) that by adding this calculated decrement to the pressure increase actually observed at end-systole, a corrected end-systolic increment in aortic pressure above the preceding end-diastolic pressure can be obtained which is proportional to the total amount of blood ejected into the aorta by that heart beat, i.e., the stroke volume.

Theoretical Considerations and Hypotheses

At the termination of systolic ejection from the ventricle, the stroke volume of that beat may be thought of as consisting of two portions: (1) a volume of blood that drained into the peripheral vascular bed during systole (the "systolic runoff"), and (2) the balance of the stroke volume, that was stored in the large elastic or capacitive arteries during this systole. The amount of blood drained from these capacitive arteries during diastole depends on the aortic pressure during diastole, the resistance to blood flow out of the large arteries, and the duration of diastole. The diastolic runoff into the periphery thus bears no constant relationship to the actual stroke volume of the preceding systole.

If the peripheral resistance vessels somehow could be occluded for the duration of systolic ejection, the total ventricular output would be stored within the arterial capacitance vessels and the pressure within these elastic arteries would be increased to a hypothetical value ($P_{hyp}$) at the end of ejection (Fig. 1).

The rise in pressure from the value at end-diastole ($P_D$) to the hypothetical end-systolic level, $P_{hyp}$, could be considered as representing a pressure increment proportional to the total stroke volume ($SV$) of this beat (Fig. 1):

$$SV \propto (P_{hyp} - P_D). \quad (1)$$

If the stroke volume is the sum of the volume of blood...
The equation could be determined if it were possible to determine APSV directly from the aortic pressure pulse.

The stroke volume could be calculated from the relationship

\[ SV = K_A \frac{\Delta PV}{SV} \]  

in which \( \Delta PV \) is the area under the systolic portion of the pressure pulse in millimeters of mercury multiplied by time in seconds. It recently has been demonstrated under a variety of hemodynamic conditions that the behavior of any given aortic diastolic decay may be characterized by a single numerical value called the "time constant" \( \tau \). This value will be most accurate if the aortic pressure pulse is recorded from a specific site in the lower thoracic aorta. \( \tau \) is the denominator of Equation 5.

The experimental procedure detailed below was designed to test the ability of the formula

\[ SV = K_A(P_{ES} - P_{D}) + \frac{SA}{\tau} \]  

to yield values for beat-by-beat stroke volumes in close agreement with those measured simultaneously by chronically implanted aortic electromagnetic flowmeters in a number of dogs.

Methods

The experimental procedures, as well as the techniques for hand and computer processing of the pressure and flow data, have been described. Six mongrel dogs with chronically implanted aortic electromagnetic flowmeters (three also had induced chronic atrioventricular block) were studied under morphine (2.5 mg/kg)-pentobarbital (15 mg/kg) anesthesia with and without control of heart rate and atrioventricular stimulus interval by means of electronically coupled right atrial and ventricular bipolar electrode-tipped cardiac catheters.

In three of the experimental studies large changes in peripheral resistance and heart rate were induced by constant-rate infusions of acetylcholine (0.5 mg/ml) and angiotensin II (A II) (2.0 mg/ml) into the arch of the aorta; the infusion rates were varied in steps. It was assumed that these vasoactive drugs, particularly A II, on reaching the large capitative arteries via the vasa vasorum, also would affect the compliance of these vessels by their actions on the vascular smooth muscle, and hence the resistance-capacitance (RC) characteristics of the arterial tree. The tip of a 60-cm, 5-Fr. Lehman catheter, with the bird's-eye tip positioned in the thoracic aorta a few centimeters cephalad to the dorsal insertion of the diaphragm, was used to record aortic pressure pulses using a strain gauge manometer (Statham P23G).

The electrocardiogram, atrial and ventricular pacing stimuli, flow velocity in the ascending aorta, pressures (multiple aortic, right atrial, right ventricular, pulmonary artery, and airway), and the amount and duration of injection of indocyanine green (1.25 mg/ml) were recorded on analog tape and converted on-line and in real-time to digital form at a rate of 200 samples/second for each channel by a computer-controlled (CDC 3300), multiplexed (100,000 ten-bit samples/second) A-D converter.

The time constant, \( \tau \), used as a measure of the steepness of the individual diastolic decays, was calculated for each pressure pulse by first sampling the diastolic pressures at 5-msec intervals. Sampling was not initiated until 30 msec after the incisura and was terminated 20 msec prior to the onset of the following systole in order to minimize errors due to perturbations in aortic pressure occurring near these two
events. Portions of any diastolic decay occurring later than 1.2–1.5 seconds after the incisura were not employed in any calculations, as it has been demonstrated that significant changes in the \( \tau \) values occur at or after these intervals, presumably due to reflex changes in peripheral vascular resistance induced by the decrease in arterial pressure associated with asystolic periods of this duration. The individual coordinate points \( (t_i, P_i) \) were plotted on a semilogarithmic scale, in which the coordinate values \( (t_i, \ln P_i) \) followed a nearly straight line with a negative slope. This set of semilogarithmic points was approximated by a standard linear regression equation \( y = mx + b \), in which \( m \) is the slope of the line and \( b \) is the ordinate intercept. The reciprocal of the slope, with the sign disregarded, was defined as the time constant \( \tau \) for the diastolic decay.

Photographic paper recordings also were taken on a sufficiently enlarged scale, either directly during each experiment or from a playback of the analog tape recordings, to allow manual analysis. Determinations of the stroke volumes by this method then were carried out on the records for each dog by a pencil-and-ruler technique, equivalent to that used by the computer, for groups of approximately 100 pulses selected at regularly spaced intervals throughout the duration of each experiment. Although it has been demonstrated that correct placement of the aortic catheter does much to ensure recordings of smooth monotonic decays of the diastolic portions of the pressure pulses, variable degrees of random beat-to-beat differences in shape as well as sporadic pressure differences do occur. Consequently, the accuracy of the calculation of \( \tau \) can be improved by the following procedure.

**METHOD FOR AVERAGING SUCCESSIVE DIASTOLIC DECAYS**

Beginning with the highest even-valued aortic diastolic pressure after the incisura, the elapsed time \( \Delta t \), needed for this pressure to fall 2 mm Hg was measured, as were the additional time segments during which the diastolic pressure fell by successive 2-mm Hg steps to the lowest even-valued pressure, or until a point 1.2–1.5 seconds after the incisura, whichever occurred first. The individually measured durations for each successive 2-mm Hg decrement in diastolic pressure were stored in the computer memory in association with the pressure value at which that change was measured. The subscript "i" represents the upper pressure of the 2-mm Hg pressure decrement over which the time increment was measured (e.g., \( \Delta t_{10} = 10 \) msec indicates that 10 msec were required for the diastolic pressure to fall from 98 to 96 mm Hg). The various \( \Delta t_i \) values from 5–10 consecutive pulses, but associated with the same even-valued pressure levels, were averaged to yield a mean diastolic decay time \( \Delta t_i \) for a decrease of 2 mm Hg to the next lower even-valued pressure level.

The analysis procedure described above was carried out by means of a computer program using as data the digitized recordings of the pressure pulses. However, this automated method is equivalent to, and was developed on the basis of, a time-consuming manual method which requires the drawing of horizontal lines spaced at even-valued pressure levels on the paper records of greatly enlarged pressure pulse tracings.

Manual measurements of the elapsed \( \Delta t_i \) between the intersections of the pressure waveform of each pulse and the horizontal lines were repeated for each group of 5–10 contiguous pulses and, as described above, a set of values for \( \Delta t_i \) were computed. Both manually and via the computer method, the successive \( \Delta t_i \) values were used to construct a single "averaged" diastolic decay curve represented by a series of even-pressure values separated from each other by the corresponding \( \Delta t_i \) values. The resultant average diastolic decay curve then was employed in the manner described earlier for the calculation of a representative time constant value \( \tau \).

Computer analyses of the dilution curves of indocyanine green for determinations of cardiac output by the Stewart-Hamilton method were carried out using the technique of Williams and co-workers. Average stroke volume \( (SV_{10}) \) was calculated by dividing the cardiac output by the average rate in cycles per minute of the first 10 heart beats after injection of the indicator into the pulmonary artery. In addition, a single in vivo calibration of the flowmeter against the indicator-dilution method was performed by comparing the sum of the areas under 10 contiguous flow pulses recorded during the duration of the indicator-dilution curve with the sum of the \( SV_{10} \) from the same 10 beats. Thereafter, beat-to-beat stroke volume values were calculated directly from the flowmeter pulses \( (SV_{FM}) \).

Systolic areas under the aortic pressure pulses \( (SA) \) were determined either by hand planimetry of the original tracings, or by trapezoid integration by the computer of the digitized \( (200 \) sample/second) aortic pressure data.

Calibration of the method was carried out against indicator-dilution measurements of the cardiac output, yielding an aortic pressure-volume conversion factor \( (K_A) \) to be employed in Equation 6. The total aortic pressure equivalent \( (\Delta P_{SV}) \) for individual heart beats was determined for each of the 10 pulses immediately after injection of indicator into the pulmonary artery; these \( \Delta P_{SV} \) values then were summed. The pressure-volume conversion factor \( (K_A) \) then was determined using Equation 3 with the indicator-dilution measurement of stroke volumes \( (SV_{FM}) \), summed over the same 10 beats, as the independent value of cardiac output.

**Results**

Figure 2 is an example of the aortic pressure and electromagnetic flow pulses and simultaneous beat-to-beat stroke volume values calculated from these two recordings. The conversion factor \( K_A \) required for the pressure pulse technique was determined for each succeeding indicator-dilution curve in order to test its consistency under the influence of the large changes in cardiac rate and rhythm plus large changes in peripheral vascular resistance induced during observation periods ranging in duration from 3 to 6 hours. Table 1 shows a summary of the average values \( (K_A) \) and lists the range and percent of standard deviation (SD) of the \( K_A \) values for each dog.

The values of \( K_A \) from different dogs varied, although in several cases \( K_A \) values for the individual dogs were within 1 SD of one another.

In an additional series of tests, only the single calibration of \( K_A \) and \( SV_{FM} \) based on the first indicator-dilution
measurement of cardiac output performed at the beginning of an experiment was used for all subsequent determinations of stroke volume by these two methods. The successive determinations of cardiac output by the dilution method at intervals throughout the experiment were used only for the estimate of SVIC and not for recalibration of the flowmeter or the pressure pulse method; hence, all succeeding SVIC, $SV_{AP}$, and $SV_{FM}$ represented values based on conversion factors determined from the first dilution curve. The series of stroke volume values extending over observation periods of 3–6 hours in six dogs are plotted in Figure 3.

Regression analyses of the sets of simultaneous values for all six dogs shown in Figure 3 were carried out for the three methods, with the values determined by the more accepted method for each set of paired values plotted on the abscissa as the independent variable. The statistics from the regression data obtained for these six dogs are summarized in Table 2. The ranges of aortic systolic, diastolic, and pulse pressures and the heart rates encountered during the periods of observation in each of the dogs are given in Table 1.

With reference to the results of Table 2: (1) The correlation coefficients were, in general, greatest in the comparisons between $SV_{AP} = SV_{FM}$ ($P < 0.001$). (2) An equality relationship of the form $SV_A = SV_B$, where $A$ and $B$ indicate any two of the methods, was often not best exemplified by the $SV_{IC}$ vs. $SV_{FM}$ methods, but rather in half of all cases, by $SV_{AP}$ vs. $SV_{FM}$ (dogs 2, 3, and 5). (3) The Y-intercepts of the regression lines were, in general, not zero, with the smallest magnitudes appearing in the relation between $SV_{FM}$ and $SV_{IC}$. (4) The SD (i.e., SYX) values were approximately the same for all methods, with a value of ±2 ml about the line.

Comparisons of variability between pairs of simultaneous stroke volume values determined by indicator-dilution, aortic flowmeter, or pressure pulse techniques reveal no clear-cut differences between the three methods. The best correlations generally were observed when the flowmeter technique was one of the methods included as a member of the pair.

Because $SV_{IC}$ is by nature a mean value, it was necessary (Fig. 3) to average the individual beat-to-beat stroke volume values obtained by the $SV_{FM}$ and $SV_{AP}$ methods over the 10 heart beats after each injection of indicator into the pulmonary artery in order to allow all three sets of values to be compared. However, every one of the paired simultaneous beat-by-beat stroke volume values determined by the pressure pulse and electromagnetic flowmeter techniques are compared in Figures 4 and 5. In each figure, the aortic pressure pulse method was calibrated only once against an indicator-dilution measurement of cardiac output at the beginning of the experiment. The variations in the stroke volumes shown in Figure 4 were induced without the infusion of vasoactive agents. The statistical data suggest the existence of an equality relationship between the two methods [slope of 1.07, Y-intercept of 0.3, SD (i.e., SYX) of 2.8 ml]. Similar relationships, which became more evident as the number of observations increased, were noted for the

Table 1 Range of $K_A$ Values and Hemodynamic Parameters Induced in Six Dogs by Intra-aortic Infusions of Acetylcholine and Angiotensin II and by Cardiac Pacing (Morphine-Pentobarbital Anesthesia)

<table>
<thead>
<tr>
<th>Values</th>
<th>Dog 1 (16 kg)</th>
<th>Dog 2 (15 kg)</th>
<th>Dog 3* (13 kg)</th>
<th>Dog 4* (14 kg)</th>
<th>Dog 5* (12 kg)</th>
<th>Dog 6 (17 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment duration, initial through final dye curve (hr)</td>
<td>6.2</td>
<td>3.3</td>
<td>3.0</td>
<td>4.7</td>
<td>3.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Number of dilution curves†</td>
<td>13</td>
<td>16</td>
<td>6</td>
<td>28</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60–186</td>
<td>56–180</td>
<td>30–160</td>
<td>45–190</td>
<td>48–180</td>
<td>52–157</td>
</tr>
<tr>
<td>Cardiac output (ml/kg)†</td>
<td>106–172</td>
<td>114–213</td>
<td>62–104</td>
<td>114–428</td>
<td>100–333</td>
<td>77–191</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>11.5–30</td>
<td>13.5–29</td>
<td>13.5–21.5</td>
<td>10.5–41</td>
<td>7.5–25.5</td>
<td>10.5–49</td>
</tr>
<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>103–153</td>
<td>110–200</td>
<td>110–157</td>
<td>110–160</td>
<td>100–165</td>
<td>95–116</td>
</tr>
<tr>
<td>Aortic diastolic pressure (mm Hg)</td>
<td>90–110</td>
<td>63–140</td>
<td>70–123</td>
<td>55–130</td>
<td>51–140</td>
<td>70–100</td>
</tr>
<tr>
<td>Aortic pulse pressure (mm Hg)</td>
<td>25–45</td>
<td>20–65</td>
<td>30–55</td>
<td>20–60</td>
<td>18–52</td>
<td>20–30</td>
</tr>
<tr>
<td>Peripheral resistance (mm Hg sec/ml)</td>
<td>2.4–6.6</td>
<td>2.5</td>
<td>1.6–7.5</td>
<td>0.7–4.6</td>
<td>1.2–7.1</td>
<td>1.8–4.7</td>
</tr>
<tr>
<td>$K_A$ (mean) (ml/mm Hg)</td>
<td>0.49</td>
<td>0.53</td>
<td>0.55</td>
<td>0.57</td>
<td>0.45</td>
<td>0.67</td>
</tr>
<tr>
<td>$K_A$ (range) (ml/mm Hg)</td>
<td>(0.39–0.55)</td>
<td>(0.38–0.64)</td>
<td>(0.50–0.65)</td>
<td>(0.44–0.70)</td>
<td>(0.34–0.65)</td>
<td>(0.55–0.79)</td>
</tr>
<tr>
<td>$K_A$ (% SD of mean)</td>
<td>10.4</td>
<td>14.3</td>
<td>10.5</td>
<td>12.1</td>
<td>16.6</td>
<td>16.2</td>
</tr>
</tbody>
</table>

* Dogs with chronic atrioventricular block.
† Total number of dilution curves throughout experiment duration.
§ Range of cardiac output values determined by arterial-dilution curves of indocyanine green dye.
two additional dogs in which vasoactive substances were not employed.

Figure 5 displays data from one of three dogs in which large changes in peripheral vascular resistance and cardiac output were induced by intra-aortic infusions of acetylcholine and angiotensin II (see Fig. 3, dog 4). A single regression line, plotted on all three panels, is based on all of the 1,900 pairs of simultaneous values obtained during this experiment, without regard to heart rate or the drug infused. The fact that this same single regression line satisfactorily represents the three different sets of data supports the existence of an equality relationship between the $S_{VA}$ and $S_{VM}$ values (slope of 1.02) under a wide range of hemodynamic conditions; this result also suggests that the value of $K_a$ in Equation 6 is not significantly altered by these changes in hemodynamic status, including alterations of the compliance of the large elastic arteries. The inclusive percent standard deviation between the two techniques is 11% about the mean value.

These results suggested that even during major changes in the hemodynamic status, beat-to-beat calculations of stroke volume by this aortic pressure method compare favorably with more "direct" methods such as electromagnetic flow measurement.

Figure 2 depicts a series of beats in which the stroke volumes varied considerably, accompanied by alterations in

**TABLE 2** Comparison in Six Dogs of Mean Stroke Volumes (ml) Calculated for Same Beats from Indicator-Dilution Measurements of Cardiac Output, Aortic Electromagnetic Flowmeter, and Aortic Pressure Pulse Method

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ordinate: $S_{VA}$ Slope</td>
<td>0.89</td>
<td>0.89</td>
<td>1.00</td>
<td>0.88</td>
<td>0.92</td>
</tr>
<tr>
<td>Ordinate: $S_{VM}$ Intercept</td>
<td>4.2</td>
<td>0.70</td>
<td>1.50</td>
<td>3.54</td>
<td>3.48</td>
</tr>
<tr>
<td>Ordinate: $S_{VM}$ $r$</td>
<td>0.93</td>
<td>0.96</td>
<td>0.94</td>
<td>0.98</td>
<td>0.91</td>
</tr>
<tr>
<td>Ordinate: $S_{VM}$ $\sigma_i$</td>
<td>0.70</td>
<td>0.97</td>
<td>1.45</td>
<td>1.54</td>
<td>1.43</td>
</tr>
<tr>
<td>Ordinate: $S_{VA}$ Slope</td>
<td>0.93</td>
<td>0.67</td>
<td>1.08</td>
<td>0.80</td>
<td>0.75</td>
</tr>
<tr>
<td>Ordinate: $S_{VM}$ Intercept</td>
<td>3.03</td>
<td>0.72</td>
<td>2.10</td>
<td>4.99</td>
<td>5.13</td>
</tr>
<tr>
<td>Ordinate: $S_{VM}$ $r$</td>
<td>0.92</td>
<td>0.79</td>
<td>0.93</td>
<td>0.94</td>
<td>0.82</td>
</tr>
<tr>
<td>Ordinate: $S_{VM}$ $\sigma_i$</td>
<td>1.72</td>
<td>2.22</td>
<td>2.40</td>
<td>2.39</td>
<td>2.00</td>
</tr>
</tbody>
</table>

* Number of observations. In each observation the values of mean stroke volume calculated by the three methods were based on the first 10 beats after injection of indocyanine green into the pulmonary artery.

† Standard deviations (ml) computed with respect to the regression lines (SYX)
the mean aortic pressure, pulse pressure amplitude, and maximal blood flow in the ascending aorta (represented by the maximal deflection of the flow pulse). The differences in flow pulse areas are directly proportional to the large beat-to-beat changes in stroke volume. These variations are especially large between the sixth and seventh pulses from the left, in which the flowmeter-calculated stroke volume decreases from 26.7 ml to 2.9 ml, with comparable values computed via the $SV_{AP}$ technique. The calibrations of $SV_{FM}$ and $\Delta P_{SV}$ were performed by a single indicator-dilution curve, carried out more than 3 hours prior to the recording of this arrhythmic burst.

**Discussion**

The linearity of the relationship between $SV_{AP}$ and $SV_{FM}$ was demonstrated for six dogs in which large hemodynamic variations were provoked continuously over periods of 3–6 hours. The relative invariability of the $K_A$ value over these durations and under the conditions of these experiments is implied by the numerical similarity of the standard deviations calculated from the entire set of data measured during short experiments as well as from those of extended duration. Further, in the sequential comparisons of the three methods with each other throughout the durations of the experiments (Fig. 3), the $SV_{AP}$ values displayed a close correlation to the other stroke volumes in all instances, although some offset was apparent in at least one dog. Since both the flowmeter and the pressure pulse methods were calibrated on the basis of a single indicator-dilution measurement of cardiac output at the beginning of the experiment, small errors during this single calibration could result in the parallel shifts observed.

Finally, graphs of the paired values ($SV_{AP}$, $SV_{FM}$) using every heart beat recorded throughout an experiment (Figs. 4 and 5) displayed a very close approximation to an equality relationship for each of the six dogs, with a Y-intercept approximately at the origin. The standard deviations about the line ($SYX$) in these figures had a maximal value of ±20% over 3–6.2 hours of uninterrupted observation, during which large variations were induced in the hemodynamic status of each dog and in the beat-to-beat stroke volume without subsequent recalibration.
This pressure pulse method thus appears to be an acceptable alternative to electromagnetic flowmetry for those cases in which instantaneous determinations of the beat-to-beat stroke volume is desired and in which conditions prevent use of an aortic flowmeter.

There is no intent to imply that the findings reported herein indicate the existence of a strictly linear pressure-volume relationship in the arterial tree over a wide range of pressures. The concept of the pressure equivalent to stroke volume, $\Delta P_{SV}$, although supported by the data of these experiments, is an artificial construct that was derived by a plausibility argument for application in the rather circumscribed manner previously discussed.

The major sources of error in this pressure pulse method are as follows: (1) An error in the automated recognition of the initiation and termination of systole which occurs most often when a computer program does not recognize accurately the onset and termination of systole. The resultant errors in the calculation of systolic area degrade the accuracy of $\Delta P_{ES}$ derived from Equation 5. (2) Errors in the determination of the time constant affect the accuracy of the right-most term in Equation 6 for the calculated stroke volume. As $r$ is used for the calculation of $\Delta P_{ES}$ only (Eq. 5), errors in the determination of its numerical value will be minimized in the final value of stroke volume by the ratio of $\Delta P_{ES}$ to $\Delta P_{SV}$. For example, in one case examined for the influence of these errors on the calculated value of stroke volume, $\Delta P_{ES}$ accounted for an average of 40% to 50% of the total $\Delta P_{SV}$, and thereby of the total stroke volume (range, 20-80%).

Calculations of stroke volume during non-steady state irregular heart beats have been found to be rather sensitive to errors in $r$, particularly if the pressure pulses are recorded from other than the optimum location in the thoracic aorta or if the computation was performed using time constants based on the diastolic decays of individual heart beats. In these instances, but also in general, the accuracy of the stroke volume could be improved substantially if $r$ were determined from an average of consecutive diastolic decays (see Methods) rather than from single beats. This is illustrated in Figure 6, for which the pressure pulse values were calculated using two different values of $r$ based on (1) the same heart beat for which the stroke volume is calculated ($SV_{AP}$), and (2) an average of the diastolic decays of the five heart beats shown in the illustration ($SV_{AP} (avg)$). The $SV_{AP}$ values calculated from the "averaged" method agree well with the $SV_{FM}$, but an additional variation of $-3\%$ to $+8\%$, referenced to the individual $SV_{FM}$ values, is present between the stroke volume determined from the "averaged" $r$ and from the single-pulse $r$ values, respectively. An additional improvement occurs when the dogs are allowed to breathe during the recording period. In most diastolic decay waveforms, even if recorded from the "optimum" location in the thoracic aorta, one or more random pressure variations of small amplitude and short duration are frequently observed, which result in a degradation of the accuracy of calculation of $r$ from the diastolic decay. The alterations in aortic pressure levels associated with changes in intrathoracic pressure during the respiratory cycle cause these small variations to be distributed more uniformly over the entire pressure range of the "averaged" diastolic decay. Another benefit accrued from these cyclical variations in intrathoracic pressure, and thereby in the baseline of the aortic pressure curve, is the cancellation of small amplitude perturbations caused by reflected pressure waves within the arterial tree. Since the relative timing of these reflected waves during the cardiac cycle is unrelated to alterations in baseline pressure, the resulting short duration increases and decreases in aortic pressure occur at a variety of absolute pressure levels in consecutive diastoles. The technique described earlier of segmental averaging of individual successive diastoles minimizes the effects of these pressure variations on the calculated average diastolic decays. The averaged $r$, therefore, is less sensitive to pressure variations than the $r$ values calculated from the individual diastolic decays.

Clinical applications of this (or any other) aortic pressure pulse technique may be more restricted than in the research laboratory because of the necessity of introducing an aortic catheter retrogradely via a peripheral vessel. The techniques requisite for maintenance of indwelling aortic catheters over extended durations, for example, in postoperative recovery environments, have become highly developed. In those instances in which aortic catheters are already in routine use, this new method may allow simultaneous monitoring of minute-by-minute cardiac output, beat-by-beat stroke volume, systemic peripheral resistance, and effective blood pressure work, either quantitatively or, if a calibration against an independent method is not available, qualitatively. As a test of the diagnostic value of the availability of such information in a real-time environment, an on-line computer program has been written for the CDC 3500 computer and is presently undergoing evaluation.

Appendix

This section demonstrates that $\Delta P_{ES}$ in Equation 2 may be represented by Equation 5, which may be applied directly to the calculation of stroke volume as demonstrated by Equation 6. The organism is considered to be in a hemodynamic steady state for the duration of one heart cycle if no asystolic period exceeds 1.2-1.5 seconds, since it has been demon-
strated that the reflex control mechanisms do not induce major alterations in peripheral resistance within a shorter time.

The blood flow rate into the periphery (Q) at the same levels of arterial pressure (P) is assumed to be the same, independent of the phase of the cardiac cycle; that is,

$$\dot{Q}_s = \dot{Q}_d,$$

where the subscripts s and d refer to events in systole and diastole, respectively, and the subscript i refers to events occurring at or near a given pressure, P. The magnitudes of the flows in Equation 7 are governed by the driving force P, via the Ohm's law analogy for liquids. Since the hysteresis factor within the large elastic arteries is small, only the magnitudes of pressure changes, and not their signs, need to be considered. The time increment $\Delta t$ is the duration required for the aortic pressure to change by a measurable amount $\Delta P$, e.g., from P, to P, +, i. The definitions of $\Delta P$ and $\Delta t$ will be refined below. It is assumed further that the volume flowing from the large arteries into the periphery is a function only of the duration $\Delta t$, over which P, is the driving force, whether during systole or diastole. The small amount of blood runoff at each P, during systole and diastole may then be represented as

Systolic runoff, $\Delta V_s = Q_s \Delta t_s$ (8)

Diastolic runoff, $\Delta V_d = Q_d \Delta t_d$ (9)

where the $\Delta t_s$ and $\Delta t_d$ are the short durations in which P, is the driving pressure. Dividing Equation 8 by Equation 9 and invoking Equation 7 yields:

$$\frac{\Delta V_s}{\Delta V_d} = \frac{\Delta t_s}{\Delta t_d}$$

(10)

If it is now postulated that whether in systole or diastole, a small change in stored blood volume in the arterial tree may be approximated by a proportional small change in arterial pressure:

$$\Delta V_i = k_i \Delta P_i,$$

(11)

and this equation is applied to events in diastole, it is possible to define a small "instantaneous pressure change equivalent to diastolic runoff, $\Delta P_{di}$" into the periphery for each P, during diastole, when the change in volume of the arterial tree is due only to peripheral runoff, the $\Delta P_{di}$ are observable values easily measured from the diastolic decay curve. Since the magnitudes of the $\Delta P_{di}$ should be small to preserve the accuracy of Equations 8-11, but are otherwise arbitrary, it is reasonable to define all $\Delta P_{di}$ to be the same magnitude. The associated $\Delta t_d$ are then the durations required for the diastolic pressure change to amount $\Delta P_{di} = \Delta P_i$, i.e., by successive small steps during which small volumes of blood $\Delta V_d$ drain into the periphery.

Although peripheral drainage also occurs during systole, the effects of this outflow on systolic pressure are masked by the inflow of blood into the arterial tree, which raises arterial pressure more per unit of time than the systolic drainage decreases this pressure. Thus, unlike in diastole, the pressure decrements $\Delta P_{si}$, the "instantaneous pressure changes equivalent to systolic runoff," are not measurable directly from the systolic curves but must be calculated from values measurable during diastole and a reformulation of Equation 10. During the time $\Delta t_s$ required for P, to increase by $\Delta P$, a volume $\Delta V_s$ drains into the periphery. If the $\Delta P_i$ in systole are chosen to be of the same magnitude as the $\Delta P_{si}$, the same absolute pressure levels P, are considered in systole and diastole, the $\Delta V_s$ and $\Delta V_{di}$ will be in proportion to the durations required for the pressure change by $\Delta P_{si}$ via Equation 10. In general, $\Delta t_s \neq \Delta t_d$ as in most cases the instantaneous rate of systolic pressure rise is unequal to the rate of diastolic decay at each P, . The small pressure rise which would have occurred during systole for each small change $\Delta P_i = \Delta P_{si}$, if no drainage had occurred, can be derived from Equations 10 and 11:

$$\Delta P_{si} = \Delta P_{di} \frac{\Delta t_d}{\Delta t_s}$$

(12)

Equation 12 allows a calculation of $\Delta P_{si}$, an artificial construct not measurable from the aortic pressure pulse, from real values of $\Delta t_s$, $\Delta t_d$, and $\Delta P_{di}$, which can be measured from the pulse. The constants of proportionality, $k_s$ in Equation 11 do not appear in Equation 12 since for any P, they are assumed to be equal in systole and diastole (assumption of minimal hysteresis), hence would appear in both numerator and denominator of Equation 12.

As a hypothetical example, suppose that a pressure change $\Delta P_i$ of 5 mm Hg was considered over the same range in systole and diastole. The limiting values P, = 105 mm Hg, and P, = 100 mm Hg, might correspond to the times $\Delta t_s = 2$ msec on the systolic segment and $\Delta t_d = 10$ msec on the diastolic segment of the aortic pressure pulse. The pressure loss resulting from the drainage from the arteries during the $\Delta t_d$ is the diastolic decay from the upper pressure level down to the lower level, that is, $\Delta P_{di} = 5$ mm Hg during the $\Delta t_d = 10$ msec.

Employing Equation 12, the hypothetical pressure equivalent to systolic runoff during the systolic pressure rise from 100 mm Hg to 105 mm Hg, as in the foregoing example, is calculated to be 1 mm Hg. That is, if peripheral drainage were prevented during systole, the pressure within the aorta would have risen from 100 mm Hg, not to 105 mm Hg, but to 106 mm Hg. Although Equation 12 is an approximation, the systematic error would be reduced significantly if a smaller pressure difference than $\Delta P_i = 5$ mm Hg had been chosen.

The determination of the individual $\Delta P_{di}$ values from Equation 12 for the successive P, values may be carried out from the onset of aortic systole, P, up to the peak systolic pressure. Extrapolation on semilog scale of the diastolic decay curves to the range of pressures up to the peak systolic pressure would be required for those values of P, greater than P, . Since it is assumed that the direction of pressure change has no effect on the arterial elastic characteristics, the calculation may be continued from the peak systolic pressure down to the pressure at end-systole, P,. Summation of all instantaneous pressure equivalents $\Delta P_{di}$ for the successive P, throughout the duration of systole yields $\Delta P_{si}$, defined as the pressure equivalent to the total drainage of
blood from the arterial tree into the periphery during systole (Fig. 1). From Equation 12:

$$\Delta P_{ES} = \sum_{i=0}^{t_{ES}} \Delta P_{d_i} = \sum_{i=0}^{t_{ES}} \left( \frac{\Delta t_{a_i}}{\Delta t_{a_i}} \right)$$

Although Equation 13 represents the rationale for the interpretation of $\Delta P_{ES}$, it is too cumbersome for direct application, particularly because of the necessity of extrapolating the diastolic decay curve up to the peak systolic pressure.

A simplified expression for $\Delta P_{ES}$ results from the derivation of an alternate form and substitution for $\Delta P_{d_i}$ on the right side of Equation 13. On the basis of the Ohm's law analogy, it is assumed that peripheral drainage out of the elastic arterial tree at any given instant is proportional to the pressure in the arterial tree:

$$\text{Flow}_i = -\frac{dV_i}{dt} = K_{si} P_i$$

If a small change in stored blood volume in the arterial tree may be approximated by a proportional small change in arterial pressure, then:

$$-AV_i = K_{si} (-\Delta P_i)$$

and in the limit,

$$\frac{dV_i}{dt} = K_{si}$$

Assuming that stored blood volume and arterial pressure are related to one another, from Equation 16 and the chain rule for differentiation, we have:

$$\frac{-dV_i}{dt} = -\left( \frac{dV_i}{dt} \frac{dP_i}{dt} \right) = -K_{si} \frac{dP_i}{dt}.$$ (17)

Substitute $-\frac{dV_i}{dt}$ from Equation 17 into Equation 14, yielding:

$$\frac{dP_i}{dt} = -K_{si} P_i$$

Form a finite difference approximation of Equation 18:

$$\Delta P_i = -K_{si} P_i \Delta t_i.$$ (19)

If this formulation is applied to the events that occur during diastole by recognizing that

$$\Delta P_i = \Delta P_{d_i}$$

Equation 19 becomes

$$\Delta P_{d_i} = -K_{si} P_i \Delta t_i.$$ (20)

Substitute Equation 20 for $\Delta P_{d_i}$, disregarding the sign, into the right side of Equation 13:

$$\Delta P_{ES} = \sum_{i=0}^{t_{ES}} \left( \frac{\Delta P_{d_i}}{\Delta t_{a_i}} \Delta t_{a_i} \right) = \sum_{i=0}^{t_{ES}} \left( K_{si} P_i \Delta t_{a_i} \right).$$ (21)

The right-most expression of Equation 21 is recognized to be a sum of small rectangles of height $P_i$ and width $\Delta t_{a_i}$ under the systolic portion of the curve, each multiplied by a different weighting factor, $K_{si}$. An immediate simplification results if all $K_{si}$ are assumed to be the same, that is, if $K_{si} = K$ for all $i$. Equation 21 can then be rewritten as

$$\Delta P_{ES} = K \sum_{i=0}^{t_{ES}} (P_i \Delta t_{a_i}).$$ (22)

The right-most term is now the rectangular integral approximation to the area (SA) under the systolic portion of the pressure curve; hence:

$$\Delta P_{ES} = K \text{(SA)}.$$ (23)

where $K$ is still to be evaluated.

The assumption that all $K_{si} = K$ imposes special constraints on the characteristics of the diastolic pressure decay. In particular, this definition in effect converts Equation 18 into a linear first-order differential equation whose solution in terms of $P_i$ is:

$$P_i = Ae^{-Kt} = Ae^{-1/w}.$$ (24)

Equation 24 is a decreasing exponential in which $K$ is the reciprocal of $w$ and $A$ represents the initial pressure of the diastolic decay at time-zero (this is the pressure $P_{ES}$ in Fig. 1). Equation 24 results directly from the assumption that $K_{si} = K$ and can only be considered valid if the actual aortic diastolic pressure decay characteristics support such an assumption. It has been demonstrated (9) that this approximation may be made with a high degree of correlation; hence, Equation 23 becomes Equation 5:

$$\Delta P_{ES} = \frac{\text{(SA)}}{w}.$$ (25)

Via Equations 2 and 5, Equation 4 thus becomes Equation 6:

$$SV = K_A \Delta P_{av} = K_A \left[ (P_{ES} - P_D) + \Delta P_{ES} \right].$$

As described earlier, oscillations provoked by aortic valve motion during the initial period of diastole are in part responsible for the characteristic shape of the incisura, including both the negative notch and thereafter the positive peak of the dicrotic wave. It is also probable that pulse wave reflections within the aorta and its major branches contribute as well to the conformation of the notch and subsequent positive wave phase. These characteristic contours, which are present even at the optimal aortic segment,* cause an underestimation of the pressure increase within the aorta at end-systole if the lowest portion of the incisura is equated to $P_{ES}$; it is possible to minimize errors from this source by choosing a mean value between the incisura and the following dicrotic peak, $P_{DP}$, called "$P_{EM}$," which is used in place of $P_{ES}$ in Equation 6:

$$P_{EM} = \frac{P_{DP} + P_{ES}}{2}.$$ (25)

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References


External Detection and Visualization of Myocardial Ischemia with $^{11}$C-Substrates in Vitro and in Vivo

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SUMMARY To characterize externally detectable changes in myocardial metabolism of free fatty acids (FFA) and glucose associated with ischemia, isovolumetrically beating rabbit hearts were perfused under conditions of selected flows with cyclotron-produced, short-lived ($t_{1/2} = 20.4$ minutes), $^{11}$C-labeled isotopes of glucose and FFA. Tension-time index decreased 83% and lactate production increased from 0.5 ± 1.9 (SE) to 5.3 ± 2.1 $\mu$mol/min per g of dry weight reflecting myocardial ischemia after flow was reduced from 20 to 5 ml/min. After 30 minutes of low flow the myocardial accumulation of $^{11}$C-octanoate, expressed as the extraction fraction, declined from 56 ± 15% to 30 ± 3%, reflecting metabolic suppression of FFA extraction during low flow. Effects attributable exclusively to prolonged residence time were excluded. Similar results were obtained with $^{11}$C-palmitate. The myocardial avidity for $^{11}$C-palmitate was demonstrable by rectilinear whole body scanning in dogs given 5 mCi of the agent intravenously. Diminished $^{11}$C-palmitate uptake in zones of myocardium rendered ischemic for 20 minutes prior to reflow in intact dogs was delineated by electrocardiographically gated positron-emission transaxial computer reconstruction tomography. Thus, diminished $^{11}$C-FFA extraction, externally detectable, accompanies decreased perfusion in isolated perfused hearts, and decreased $^{11}$C-FFA uptake reflecting myocardial ischemia in vivo can be evaluated noninvasively by positron-emission transaxial tomography.

THE NEED to detect and estimate the mass of ischemic myocardium in vivo has given impetus to the development of several approaches. The presence and extent of impaired contractility, altered ventricular diastolic compliance, and ventricular dyskinesis have been used as indirect indices of the severity of ischemic insults.1 Electrophysiological alterations have proved useful functionally but suffer from quantitative limitations.2 Although ischemia can be inferred from analysis of coronary artery anatomy or detected in coronary sinus or peripheral blood, provide only gross indices of altered metabolism or tissue integrity and do not localize or quantify reversible or irreversible injury.3

During the past two decades the metabolic characteristics of normal and ischemic myocardium have been clarified substantially. Data have been gathered primarily in studies of coronary arteriogenous differences and in investigations of substrate utilization in isolated perfused hearts subjected to selected physiological conditions.4* In general, aerobic myocardium preferentially utilizes free fatty acid (FFA) for energy production. In contrast, FFA oxidation ceases in anoxic or severely ischemic tissue and glycolytic flux increases at least transiently. However, the effect of tran-
Continuous determination of beat to beat stroke volume from aortic pressure pulses in the dog.

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