Coherence of cardiac output with rate changes

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MELBIN, JULIUS, DAVID K. DETWEILER, ROBERT A. RIFFLE, AND ABRAHAM NOORDERGRAAF. *Coherence of cardiac output with rate changes.* Am. J. Physiol. 243 (Heart Circ. Physiol. 12): H499–H504, 1982.—In awake or lightly anesthetized dogs increases in heart rate (HR) induced by atrial pacing affect cardiac output (CO) and stroke volume (SV) in a predictable way that is represented by a SV-HR relationship (dSV/dHR). Under our experimental conditions where normal regulation of atrial rate was bypassed, atrial rate was the independent variable and CO and SV were dependent variables. As HR is increased, CO and SV are modified by reflex and other circulatory regulators. The dSV/dHR relation characterized the circulatory response to increasing HR. A single dSV/dHR curve consistently predicted responses under a number of different conditions (standing, recumbent, awake, various anesthetics, β-adrenergic stimulation, or depression) and thus appeared as an expression of cardiac function. Alterations of the circulation by stellate ganglion or vagal stimulation, volume loading, aortic compression, and ventricular pacing were not represented by the same dSV/dHR function. The dSV/dHR function (including its linear version as reported by others for anesthetized dogs) showed that, when SVs were larger at low rates, maximum CO occurred at a higher HR. Recognition of this arithmetic-based feature resolves apparent contradictory findings reported in the literature.

stroke volume; heart rate; maximal cardiac output; atrial pacing

THE INTERACTION OF THE HEART with other components of the circulatory system, recognized by Roy (21) as early as 1879, obscures individual functional properties. Alterations in ventricular filling, in the state of the arterial system, and in the heart's contractile properties influence blood pumping (24). These parameters may be altered with changes in heart rate and respond to metabolic and neurogenic controls (22). Thus the dependency of cardiac output on heart rate is complex (15, 20, 29).

To illustrate, Kumada et al. (12) observed in atria-paced dogs that cardiac output (CO) could increase, decrease, or remain unchanged with increasing heart rate (HR), whereas Ross et al. (20) found CO to be virtually constant in humans at rest despite large atria-induced changes in HR. They attributed the differences to the manner in which stroke volume (SV) reduced with increasing HR. At any HR, left stellate stimulation and blood volume expansion augmented CO, whereas vagal stimulation and aortic compression reduced CO. Others have noted [in atria-paced conscious dogs (15) and normal patients (23)] that, unlike CO, SV decreased consistently with increases in HR. Noble et al. (15) attributed the reduction principally to a loss in late systole. Hung et al. (8) associated the reduction in SV (in atria-paced human patients) to a reduction in end-diastolic volume and reported that the ejection fraction remained relatively constant.

Vatner and Boettcher (28) reported that, in the reclining dog with low control HR, increases in CO resulting from volume loading were due to an increase in HR. In contrast, in anesthetized open-chest dogs with high control HR accompanied by low SV, volume loading produced CO elevations almost entirely as a result of SV increases. They noted that in the group with low HR ventricular size was near maximal so that volume loading only slightly increased ventricular dimensions, whereas in the group with high HR, volume loading markedly increased the initially small volume. It has also been observed in humans during exercise or isoproterenol infusion that CO can be increased by an increase in SV when HR is held constant or by an increased HR when HR is not controlled (20).

Sugimoto et al. (27) also associated impaired ventricular filling with the reduction of CO accompanying increasing HR in atria-paced, vagotomized dogs. Increased filling pressures and infusion of norepinephrine increased the HR at which maximal CO occurred. Clinical observations (30) confirmed that filling pressure significantly influences the CO-HR relation. In ventricle-paced dogs with arteriovenous fistulas, the HR at which CO is maximal was shifted to higher values in response to increased venous return, infusion of norepinephrine, or sympathetic stimulation (3). An extensive compilation (18) reported as much as two- to threefold increases in both CO and HR with volume increases.

Ilebekk et al. (10) examined anesthetized, atria-paced dogs over a range of relatively high HRs (about 125–325 beats/min) and reported that β-receptor stimulation (infusion of isoproterenol) increased SV and HR, whereas β-receptor inhibition (infusion of propranolol) decreased SV and HR. They demonstrated that the change of SV with HR (i.e., the derivative of the SV-HR relation, dSV/dHR) remained unchanged. Conversely, blood volume expansion (saline infusion) altered dSV/dHR, but the HR at which CO reached its maximum remained essentially unchanged.

Based on this and previous work (9) they concluded that *1*) chronotropic changes influence end-diastolic volume; *2*) inotropic changes influence end-systolic volume; *3*) the effects are virtually independent; and *4*) the effects are distinguishable by noting the course of dSV/dHR vs.

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HR. They regarded as unlikely the interpretation by others (3, 27) that the shift in HR at which CO is maximal is due exclusively to preload alterations.

The role of HR as a determinant of CO has been investigated using both atrial and ventricular pacing sites. Because CO is also dependent on the site of ventricular pacing (13), a less complicated perturbation is provided with atrial pacing (7). Generally, CO increases with HR at low HR, is relatively insensitive to HR at intermediate HR, and decreases at high HR. Similar relationships have also been demonstrated with ventricular pacing (6, 14, 29).

It is generally assumed that the SV-HR relation is linear (8, 10, 15, 20, 26). A linear relation, however, can only be applied in a limited range of HR, otherwise it would lead to unattainable physiological responses. Also, as anesthesia interferes with neural control systems, CO-HR relationships may differ in the awake state. In the study reported here a coherent CO-HR relationship was found in awake and anesthetized dogs.

METHODS

Instrumentation. Seven mongrel dogs, weighing between 15 and 24 kg, were instrumented chronically with an electromagnetic flow probe (around the root of the aorta) and with a radiopaque no. 5 French catheter. The latter was introduced via the internal thoracic artery into the root of the aorta with the tip located at the center of the flow probe. A Statham transducer (SP-37) provided manometric data. In addition, a bipolar electrode (Medtronic or modified Medtronic type) was sutured to the right atrial appendage. All leads and the catheter were placed subcutaneously and exteriorized through skin connectors along the thoracic spine (caudal to the scapulae). A pacing stimulator of our design, operating in constant current mode, provided square pulses of about 2 mA for 2 ms.

Data acquisition. A lead II electrocardiogram, root aortic flow, and pressure were recorded (on FM magnetic tape) during control (prepaced) and paced periods. Data were recorded with the dogs under light anesthesia at the time of surgery, and over a period of days with the unanesthetized animals lightly restrained (standing) by a support sling. Depending on animal condition, about 2–4 days elapsed after surgery before data were acquired from the awake animal.

To ensure capture, stimulation frequency commenced at 10 beats/min above the prepaced rate; this continued for at least 2 min. Pacing was then increased by 10 beats/min in successive trials. Pacing rate was decreased in similar steps.

Data processing. The data yielded HR and SV (integrated flow) which were recorded on a calibrated chart recorder and as scatter plots. Pressure and SV data from each experiment for a particular dog on a particular day were averaged for each HR separately. The value of the averaged mean pressure corresponding to 150 beats/min was used to normalize mean pressure across the HR range. Standard errors were determined. This provided a measure of pressure among the animals and with changes in HR. In addition, SV averaged from each experiment for each HR was used to derive dSV/dHR (the slope of the SV-HR curves). dSV/dHR at each HR was derived from data for rates just above and below that HR. All slopes from all experiments were then averaged for each HR and the standard errors determined. These slope data were least square regressed to the lowest (2nd) order polynomial that characterized the nonlinear distribution, and the correlation coefficient was determined. This data reduction process provided a single representative dSV/dHR expression for all experiments.

The single slope expression, integrated once with respect to HR, relates SV to HR for a variety of integration constants (discussed below). This latter expression multiplied by HR yields CO as a function of HR.

RESULTS

Rate response. The HRs, whether during control or paced periods, ranged from 64 to 250 beats/min. The incidence of blocked beats in the awake animal increased, as expected, as the pacing rate increased above the animal's prepaced HR (6). For any prepaced HR, a one-to-one response was always achieved, up to a pacing rate of about 20% greater than the prepaced HR. Blocked beats did not occur, regardless of the prepaced HR, when the animal was anesthetized with halothane.

As the prepaced HR increased, the ventricular rate approached the paced rate; i.e., the number of blocked beats decreased. For prepaced HRs of about 80 beats/min or below, maximal ventricular rates were on the order of 50% greater than the prepaced HR. As HR was increased by pacing, a one-to-one conduction was approached and could generally be expected with prepaced HRs above 90 beats/min. At the higher prepaced HRs spontaneous sinus discharge sometimes prevented atrial capture by the pacemaker.

Stroke volume response. Figure 1 illustrates raw data from a dog, acquired over a period of days under apparently similar circumstances. Stroke volumes used were drawn from segments of steady-state data when ventricular rate equalled pacing rate; i.e., dropped beats were not used in the characterization. Solid lines represent data acquired during awake periods, and dotted lines represent data acquired during light halothane anesthesia. Open circles are control data. This illustration is representative of all animals in the study. Variation of both prepaced SV and HR was observed in repeat experiments (on different days and on the same day) in spite of apparently similar circumstances. Day-to-day variations have been reported previously, even with apparent behavioral inactivity (4, 5, 7). In contrast, the slopes were more consistent, regardless of whether the animal was awake or anesthetized. Stein et al. (25) reported similar findings in humans.

Figure 2 illustrates mean pressure and dSV/dHR over the range of HR. Because data below 80 and above 230 beats/min were scant, the analysis was limited to this range. In Fig. 2*A*, the points represent pressure data from all experiments, each normalized to its respective value at 150 beats/min and subsequently averaged. Figure 2*B* illustrates dSV/dHR derived from all experiments, as described in the methods section. Vertical lines are standard errors of the means.

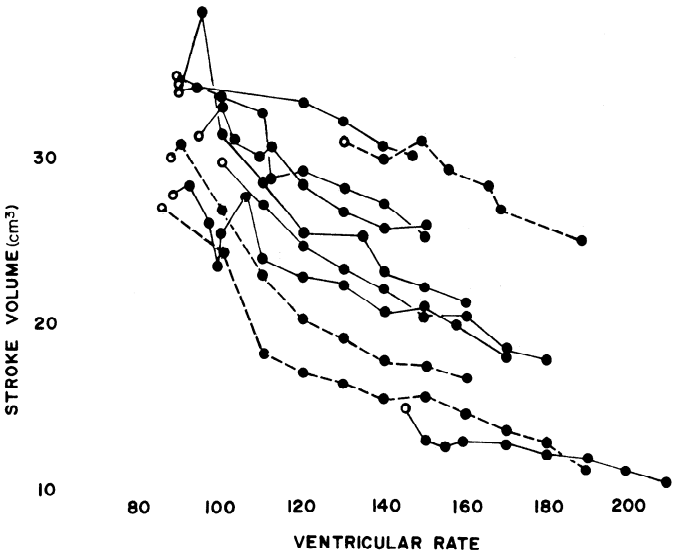

FIG. 1. Raw data from 1 dog acquired over a period of days under apparently similar environmental circumstances. Similarity in stroke volume-rate slopes persists within a wide range of rate and stroke volumes.

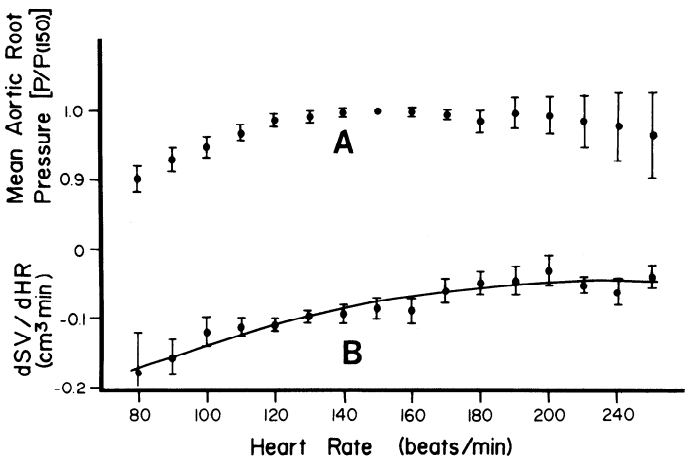

FIG. 2. *A*: mean root aortic pressure. Data from each expt normalized to mean pressure at 150 beats/min. *Vertical lines* are SEM. *B*: slope of stroke volume (SV) vs. heart rate (HR) for all expts; i.e., dSV/dHR shown as data points at each rate. *Solid line* is quadratic regression function. (*Equation 5*, with $c_1 = -0.63 \times 10^{-5}$ cm^3·min^3, $c_2 = 0.279 \times 10^{-2}$ cm^3·min^2, $c_3 = -0.353$ cm^3·min for segment shown).

At lower rates dSV/dHR scatter was greater. In some dogs reduced slopes characterized that segment. It has been shown in dogs with heart block paced via the right ventricle that SV appears relatively constant at rates below 60 beats/min (13). Evidence for this also appears in other data (Fig. 5).

Figure 3*A* illustrates the slope function dSV/dHR, the fully drawn regression line from Fig. 2*B*. Except for an integration constant integration of this function yields SV itself as a function of HR. The integration constant in our data range was drawn from the known SV at 80 beats/min (SV_{80}). Each SV-HR function was normalized with respect to its SV_{80} and the results plotted in Fig. 3*B*. The value of SV used for normalization is shown to the right of each curve.

Although the data may be normalized to any reference value [e.g., Kumada et al. (12) used 160 instead of 80 beats/min], the rate selected permitted the simplest display of the data. Figure 3*B* shows that SVs were largest at 80 beats/min and that the smaller this value the more rapid was the decline with increasing HR.

CO obtained by multiplying SV (Fig. 3*B*) by HR is illustrated in Fig. 3*C*. Each curve is normalized with respect to its maximum. The parameter values indicated for each curve are the SV_{80} values as in Fig. 3*B*. Figure 3*C* demonstrates that maximum CO occurs at a higher HR the larger its associated value of SV_{80} is, a phenomenon observed experimentally (10).

Thus depending on the value of SV_{80} and the range of HRs, CO may increase, decrease, or remain essentially unchanged. This not uncommon finding (4, 5, 7) is illustrated for a typical dog in Fig. 4 for data collected on two different days under apparently similar circumstances (dots, experimentally observed values; lines, predicted

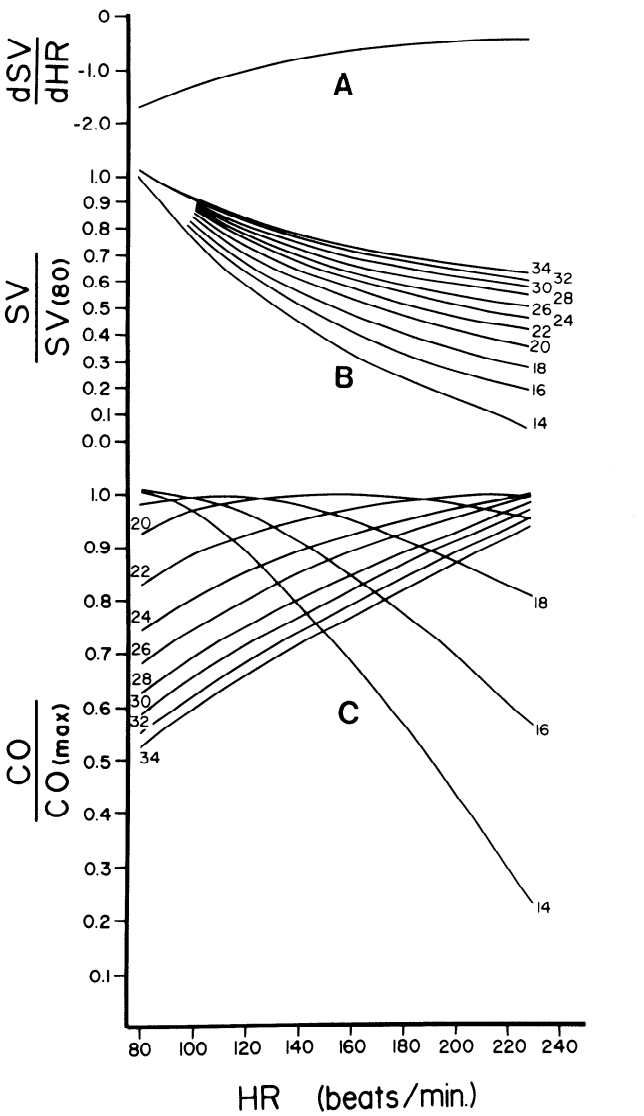

FIG. 3. *A*: quadratic regression function representing stroke volume-heart rate (dSV/dHR) data for all expts (from Fig. 2*B*). *B*: family of curves resulting from integration of slope function for different constants of integration. Curves displayed as ratio of actual SV to SV at 80 beats/min. Parameters are stroke volumes at 80 beats/min. *C*: family of curves resulting from multiplication of SV by rate to yield cardiac output (CO) each normalized to their respective maximum CO value. Parameters identify output curves with associated SV ratio curves.

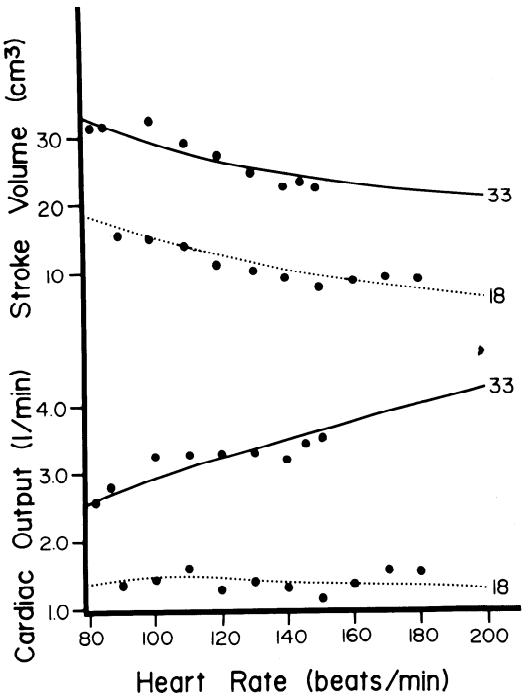

FIG. 4. Data from a single dog for 2 different days. *Lines through data points* derive from single slope function (Fig. 3*A*).

from Fig. 3*A*). The two values of SV at 80 beats/min are shown as parameters.

It should be emphasized here that the SV and CO dependence on HR displayed in Figs. 3, *B* and *C*, and 4 were all derived from the same dSV/dHR curve shown in Fig. 3*A*. Inasmuch as derived relationships may be expected to fit the source data, the applicability of this single dSV/dHR function to data of other investigators was examined. Figure 5 illustrates data points (filled and open circles) taken from the literature (12). This source was chosen because the authors measured SVs in dogs (anesthetized) that were paced via the right atrium, similar to those of our study. In addition, this group imposed interventions that altered rate responses of SV and CO. In Fig. 5 the filled circles are the control data points of Kumada et al. (12), and the open circles are the consequences of their perturbations. The solid curves were calculated from our dSV/dHR function as in Fig. 3*A*, i.e., are predicted from our data. All data were normalized to the value at 160 beats/min, the reference used by Kumada's group.

The data points in Fig. 5*A* were presented by Kumada et al. as one example of the experimentally observed relation between HR, SV, and CO. Figures 5, *B–E* demonstrate control data (filled circles) each compared to the response to a perturbation (open circles). These perturbations were, respectively, left stellate ganglion stimulation (Fig. 5*B*), bilateral cervical vagus stimulation (Fig. 5*C*), infusion of isotonic dextran saline solution (Fig. 5*D*), and a sudden sustained increase in peripheral resistance through partial compression of the thoracic aorta (Fig. 5*E*). The solid lines in each case derive from our single dSV/dHR function (for our unperturbed animals) and is seen to represent all the control data but not these interventions.

Pitt and Gregg (19) illustrated a rate response in an unanesthetized dog that was paced via the apex of the right ventricle. Our dSV/dHR function (Fig. 3*A*), derived from a right atrium pacing protocol, did not provide a suitable representation for this data. This is not surprising in the light of the results obtained by Lister et al. (13), who reported that the ventricular pacing site in dogs significantly influences CO. Conversely, the dSV/dHR function provided a good representation for an example illustrated by Noble et al. (15) for a conscious dog, paced via the right atrium, and for an example by Ilebekk et al. (9) for right atrial-paced, anesthetized animals (for control data and data resulting from either isoproterenol or propranolol infusion). The function did not, however, predict data (of this latter group) which represented responses to blood volume expansion.

DISCUSSION

Stroke volume and rate dependency. From experimental findings it is clear that a maximal CO exists and is reached with different HRs under different circumstances. A coherent basis for the interpretation of CO-HR behavior for different physiological states has not evolved despite numerous experimental studies. The

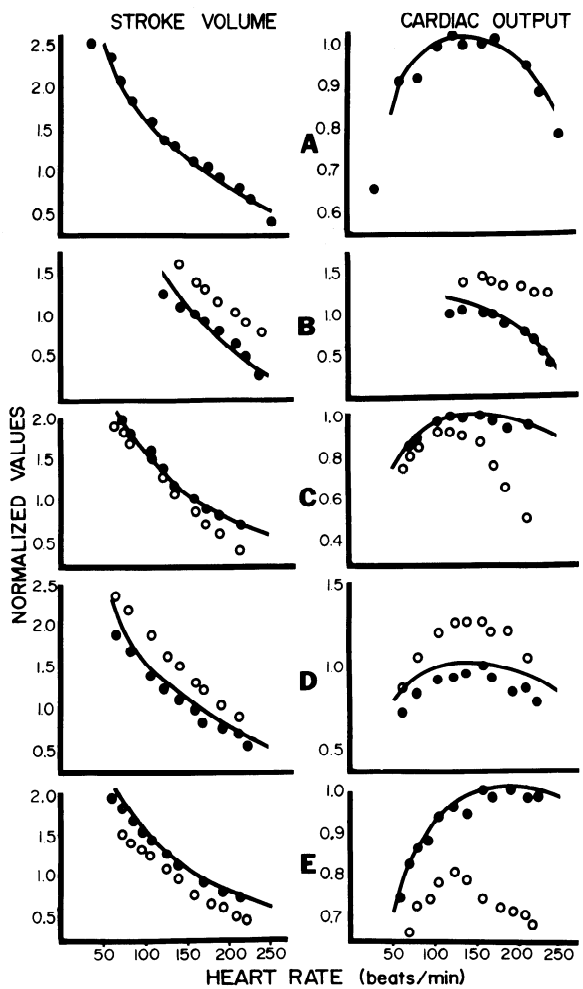

FIG. 5. Data (dog) from literature (12). *Filled* (control) and *open* (perturbed system) *circles* are data points normalized to their value at 160 beats/min. Lines are derived from our single-slope function (*Eq. 5*) representing the resting animal.

most elementary function that expresses such behavior is a second-order polynominal of the form

$$CO = -aHR^2 + bHR \quad (1)$$

where a and b are positive constants.

On the basis of *Eq. 1* stroke volume follows as

$$SV = -aHR + b \quad (2)$$

and

$$dSV/dHR = -a \quad (3)$$

In view of the interactive participants it would be expected that dSV/dHR is HR dependent, rather than a constant (as in *Eq. 3*). Even with the simple linear function of *Eq. 2,* however, the essence of the CO-HR response as seen in Fig. 3*C* would be manifest (10, 16). A number of workers have regressed their experimental SV data to this linear function (8, 10, 15, 20, 26). The maximum value of CO occurs at a HR (HR_{max}) that follows from *Eq. 1,* i.e. HR_{max} where dCO/dHR = 0 (17). Hence

$$HR_{max} = b/2a \quad (4)$$

The slope function (*Eq. 3*), however, cannot be a constant over the entire frequency range as its integrated form (*Eq. 2*) would then imply a zero crossing and consequently negative SV at some range of high HRs. This flaw resides, for example, in the report of Ilebekk et al. (10), if pacing was extended to the highest HR for animals perfused with isoproterenol.

dSV/dHR could also not be a linear function of HR with positive slope, as this would lead to increasing SV with increasing HR for all HRs. All experimental data suggest that the dSV/dHR function tends toward zero at high HR. Even a quadratic expression in HR, which offers a reasonable lowest order descriptor (*Eq. 5*) for our data range, does not achieve zero asymptotically. Also, evidence that SV is relatively constant at HRs below 60 beats/min (13) implies a minimum and an inflection point in the dSV/dHR function.

Interpretation of regression function. The nonlinear distribution of our dSV/dHR function prompted regression to the second-order polynomial

$$dSV/dHR = c_1HR^2 + c_2HR + c_3 \quad (5)$$

where c_1, c_2, and c_3 are constants (correlation coefficient $r = 0.961$). The expression represents our discrete data in the HR range and provides mathematical tractability, continuity, and data reduction. Without additional information the coefficients c_1, c_2, and c_3 do not have physiological meaning. Because the choice of the function determines the accuracy to which the data are represented, regression functions emphasize data distribution rather than complete numerical reproduction. As biological data are generally scattered, this is often inconsequential. Regardless of the function utilized for regression, extrapolation beyond its data range need not provide meaningful data.

The expression for dSV/dHR in *Eq. 5,* with its coefficients unchanged, was employed to derive all curves in Figs. 3, *A–C,* 4, and 5. Consequently, it can be seen that what may appear as contradictory behavior of CO with HR (as cited in the introduction) simply follows from the form of the dSV/dHR expression. That is, once dSV/dHR is established by virtue of SV-HR responses, CO follows from arithmetic relations and need not be cast separately in terms of physiological responses (17).

If dSV/dHR accurately represented the entire frequency range (rather than our limited range of 80–230 beats/min), the integration constant appearing in the SV-HR relationship (e.g. *Eq. 2*) may have physiological meaning, i.e., the potential maximum SV (the maximum SV achievable as HR decreases) unaffected by filling time for a given circulatory state. In this sense the potential maximum SV could be a descriptor of the circulatory state.

System aspects. The dependence of SV on system parameters (such as circulating blood volume, the state of the vasculature, peripheral resistance, and metabolic controls) is embodied in preload (P), afterload (A), and contractile properties (C), as discussed in the introduction. Hence SV may be altered by a change in each quantity acting alone or in concert. Independent control of HR, as done in this and other studies, removes HR from system control. Thus a corollary to *Eq. 5* defining the total change in SV with HR appears as

$$\frac{dSV}{dHR} = \frac{\partial SV}{\partial P}\frac{dP}{dHR} + \frac{\partial SV}{\partial A}\frac{dA}{dHR} + \frac{\partial SV}{\partial C}\frac{dC}{dHR} \quad (6)$$

Therefore, the total change of SV with HR is dependent on the effect of HR on P, A, and C.

The present study yielded an expression representing the left-hand side of *Eq. 6.* It also demonstrates that more than one state of the system is accommodated by the same expression in *Eq. 5,* despite Fig. 2*A* suggesting that individual terms on the right-hand side of *Eq. 6* alter with HR. Conversely, certain perturbations cause the circulatory system to depart from the dSV/dHR expression (*Eq. 5*) developed from our data.

States accommodated by *Eq. 5* include those of our animals (either under anesthesia or awake and standing quietly), those of Noble et al. (15) (awake and lying quietly), and those of Kumada et al. (12) and Ilebekk et al. (9, 10), whose animals were also anesthetized. Three different anesthetic regimes are represented; i.e., pentobarbital sodium, thiopental-halothane, thiopental-chloralose-urethane, as well as two pharmaceutical interventions, i.e., isoproterenol and propranolol. States not represented by our expression include volume loading, stellate ganglion and vagal stimulation, sudden aortic compression, and responses to ventricular pacing. Presumably, other states (e.g., exercise, disease) may also require their own dSV/dHR functions.

In the same animal at the same HR, SV can vary under apparently similar external circumstances, so that the CO response to cardiac acceleration is altered. Regulatory mechanisms that maximize SV relative to HR augment the effect of positive chronotropy and elevate the HR at which maximal CO occurs (6, 27). There are some clinical implications of these CO-HR responses. Skelton and Sonnenblick (23) consider HR to be a major determinant of myocardial energy utilization. Thus an attempt to increase CO by increasing HR may be imprudent without assurance that the ventricle will not operate in the descending limb of its CO-HR response. Conversely,

more optimal CO-HR responses for certain circumstances may be realized, e.g., the use of propranolol following cardiac infarction (11), by permitting equivalent CO to be attained at a lower HR. Also, alteration of afterload to relieve heart work by pressure reduction could be self-defeating if normal responses act to increase HR (1, 2) and the ventricle enters an adverse operating mode.

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