A COMPARISON OF METHODS OF EVALUATING MYOCARDIAL CONTRACTILITY

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GLOSSARY

V. max The peak or maximum velocity of blood. In this paper the observations are taken from the descending aorta.

Q. max The peak or maximum flow of blood. In this paper the observation was taken from the descending aorta.

dP/dt max The maximum rate of rise of pressure within the left ventricle during the isovolumetric phase of myocardial contraction.

dQ/dt max The maximum rate of change of flow in the descending aorta.

dV/dt max The maximum acceleration of blood moving in the descending aorta.

I.P. The instantaneous developed pressure at the time of maximum dP/dt; observed pressure at the time of dP/dt max minus the end diastolic pressure. In this paper the observations are taken from the left ventricle.

I.Q. The instantaneous flow at the time of dQ/dt max. In this paper the observations are taken from the descending aorta.

I.V. The instantaneous velocity at the time of dV/dt max. In this paper the observations are taken from the descending aorta.

dP/dt ÷ I.P. The pressure, myocardial contractility index; its units are in l/time.

dQ/dt ÷ I.Q. The flow, myocardial contractility index; its units are in l/time.

dV/dt ÷ I.V. The velocity, myocardial contractility index; its units are in l/time.

dV/dt max ÷ V. max. The peak velocity myocardial contractility index; this index compensates for the effects of afterload; that is, peripheral resistance on the acceleration of the blood.

l/PEP The reciprocal of the Pre-Ejection Period; that is, the period of time between the start of ventricular systole and opening of the aortic valve. This corresponds to the iso-volumic phase of ventricular contraction. This reciprocal is also in l/time units.

SINCE THE DEATH of Hannah Greener in 1846, a few weeks after the introduction of chloroform, there has been a growing awareness of the need to monitor various aspects of the circulation during anaesthesia. The progression of investigation has been, first, observation of the pulse, then recording the changes in blood pressure, continuous display of the E.C.G., and finally attempts to assess the inotropic state of the heart. In this latter effort, the term "myocardial contractility" is frequently used. This designation, however, has many meanings, e.g., isometric tension,[1] increased velocity of contraction,[2] and increased force of contraction.[3]

Rushmer[4] has propounded a general principle: that rates of change are significantly larger with increases in myocardial contractility, as compared with the

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absolute changes of the other units. This rule applies to whatever parameter is being measured, whether in pressure units and their rates of change, dP/dt, flow units and their rates of change, dQ/dt, or work units and their rates of change, i.e., power.

It is because pressure is easy to measure that attention has focused on assessing myocardial contractility in terms of the maximum rate of change of pressure within the ventricle, that is, dP/dt max. However, the invasive approach that is required is not suitable for patient care. The development of the electromagnetic flow meter as a laboratory tool has stimulated interest in the measurement of blood flow as an index of myocardial contractility, but, again, an invasive technique is necessary. Recently, the Pre-Ejection Period has been suggested to provide a correlate with myocardial contractility.[5] Out attention has been attracted to the Doppler shifted ultrasound signal, that is derived transoesophageally from the descending aorta, as a determinant of blood velocity. It is possibly another index for assessing myocardial contractility.

The use of absolute rates of change as indices of myocardial contractility has been questioned on the grounds that these rates are affected by myocardial preload (or end-diastolic pressure or volume) and afterload (or diastolic pressure).[6,7] Ratios have been suggested, e.g., max dP/dt ÷ I.P., where I.P. is the instantaneous developed pressure. All ratios result in 1/time units, as does the reciprocal of the Pre-Ejection Period. Because of this correlation, we decided to compare ratios of the various signals produced through the four described techniques to test the level of agreement between them as they pertain to myocardial contractility.

METHODS

Anaesthetized and mechanically ventilated dogs were studied. The experimental protocol by which the measurements were made has been described elsewhere.[8] In our work, the following parameters were obtained:

(1) dP/dt max.[9] Stringent criteria for the measurement of this parameter have been established if catheter-tipped manometers are not available. The key criterion was that the 95 per cent amplitude frequency response of the measuring system should be better than 20 times the heart rate. This determination was verified for our equipment by Polaroid photography of the oscilloscopic display of the pressure changes resulting when a water-filled balloon, placed on the end of the cannula and transducer system, was burst. Subsequent calculation of the oscillations of the resulting pressure waves and the rate of their decay enabled the damped frequency, natural frequency, damping ratio, rise time, overshoot, and 95 per cent amplitude frequency response[10] to be determined. Results are given in the appendix. The system was capable of obtaining faithfully dP/dt, within the specification desired.[9] The electronic differentiation of the pressure signals was displayed on a Hewlett-Packard pen recorder. These signals were obtained by means of a short (3″–4″), wide-bore (I.D. 1.5 mm) cannula pushed through the wall of the left ventricle and attached to a Statham P37 transducer. The mean of the steepest tangents was measured manually from the records of intraventicular pressure of five consecutive cardiac cycles and compared with the

mean of the signals of dP/dt max from a differentiator for the same five cardiac cycles. This technique was repeated over a wide range of dP/dt max to enable a complete calibration curve to be obtained. This same procedure was performed for every animal study. The intraventricular pressure at the point of maximum dP/dt was also noted, as was the end-diastolic pressure, and the difference between the two is defined as the instantaneous developed pressure (I.P.).

(2) dQ/dt max. This ratio was obtained manually by measuring the steepest tangent of the flow signal obtained from a Hewlett-Packard electromagnetic flowmeter probe placed around the ascending aorta. The mean dQ/dt max was taken for five consecutive cardiac cycles on each occasion. The instantaneous flow at the point of maximum dQ/dt was also obtained as was peak flow.

(3) dV/dt max. The velocity signal was obtained by means of a transoesophageal ultrasound velocity probe and a Parks 803 Doppler velocity meter. The probe tip was inserted to a point just above the diaphragm and it directed an 8 MHz beam of ultrasound against the descending aorta. The demodulated, Doppler-shifted, back-reflected beam of ultrasound was the velocity signal. Calibration of the Doppler shift was accomplished by means of a second electromagnetic flowmeter placed around the descending aorta just above the position of the ultrasonic probe. Calibration of the differentiator was performed in the same manner as that of the pressure channel differentiator, e.g., the mean of the steepest tangent (drawn manually) of the velocity signal of five consecutive velocity cycles was compared with the differentiator output and a calibration curve was constructed by repeating this process over a wide range of max dV/dt. Instantaneous velocities at the time of max dV/dt and peak velocities were both recorded.

(4) P.E.P. The Pre-Ejection Period was also measured. Though this technique can be accomplished by a non-invasive means, for convenience the time relations of the signals obtained by the invasive technique were used. P.E.P. was taken as the difference in time between the onset of the intraventricular pressure wave and the onset of flow in the ascending aorta as indicated by an electromagnetic flowmeter probe placed in this position.

Myocardial contractility was then varied by the administration of drugs, such as epinephrine, nor-epinephrine, calcium chloride, neostigmine, and trimetaphan, as well as by haemorrhage, hypotension, and by severe hypoxia. The objective was to produce a wide range of derangements of myocardial contractility, although differences could not be quantified except by analogue interpretation of such indices as max dP/dt ÷ I.P.

RESULTS

For each dog, a linear regression analysis was performed using the least-squares technique. Each of the parameters was compared with all others. First compared was dP/dt max versus dQ/dt max, dV/dt max, and 1/PEP. All data points used in the regression analysis were the mean of the same set of five consecutive cardiac cycles. For technical reasons, it was not possible to obtain data points on every parameter on every occasion. Indeed, as Table I indicates, in one experiment there was a total failure of one channel which, of course, did not

TABLE I

	Max dP/dt – vs. –						Max dQ/dt – vs. –				Max dV/dt – vs. –	
	Max dQ/dt		Max dV/dt		1/PEP		Max dV/dt		1/PEP		1/PEP	
Dog	n	r	n	r	n	r	n	r	n	r	n	r
1	10	0.879	9	0.539	10	0.905	9	0.666	0	0.886	9	0.511
2	10	0.867	10	0.880	10	0.708	10	0.702	10	0.831	10	0.633
3	10	0.946	10	0.383	10	0.066	10	0.405	10	0.068	10	0.444
4	3	0.975	10	0.197	3	0.081	3	0.937	3	0.297	3	−0.053
5	8	0.964	4	0.371	9	0.686	3	0.933	8	0.896	4	−0.466
7	11	0.438	11	−0.171	11	−0.141	11	0.531	11	−0.067	11	0.181
8	6	0.605	11	−0.017	6	0.583	6	−0.095	6	0.741	6	−0.368
9	—	—	8	0.708	8	0.019	—	—	—	—	8	−0.197
10	13	0.763	13	0.083	13	0.444	13	0.269	13	0.165	13	−0.427
11	15	0.770	15	0.521	15	0.675	15	0.820	15	0.870	15	0.751
Mean *r		0.7845		0.3309		0.3597		0.546		0.5212		0.194
Total N		86		101		95		80		86		89
Student t.		10.95		3.307		3.4906		5.423		5.2175		1.735
P		0.0005		0.0025		0.0025		0.0005		0.0005		0.05
Binomial Probability (of a positive association between the two parameters).												
N		9		10		10		9		9		10
r		0		2		1		1		1		5
p		0.0019		0.044		0.0097		0.017		0.0171		0.246

Individual correlation coefficients, and *weighted mean correlation coefficients and their statistical significance, together with the Binomial Probabilities.

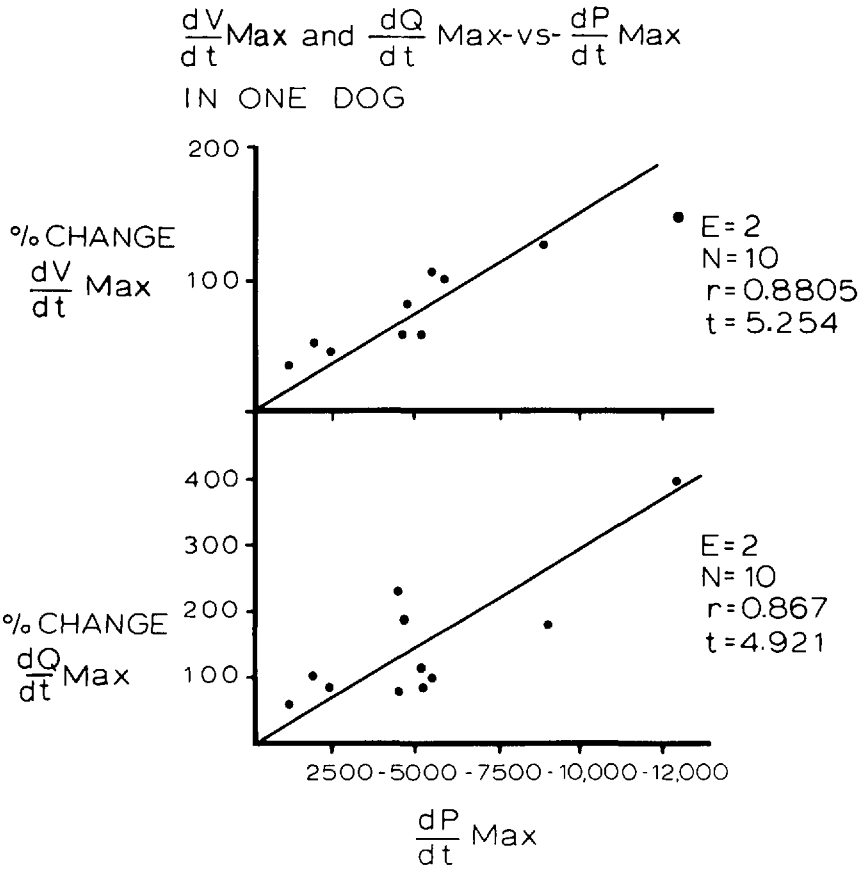

FIGURE 1. The acceleration of blood in the descending aorta as determined by a Doppler shifted ultrasonic signal, dV/dt, and the electromagnetically measured flow, dQ/dt is compared with the rate of change of pressure within the left ventricle.

affect the validity of the comparisons obtained from the other channels. Table I lists the experiments, the number of observations for the individual experiments and the individual correlation coefficients. An example of the linear association observed between dP/dt and dQ/dt and dV/dt is given in Figure 1.

To derive a comparison between two parameters from all the data, the weighted mean correlation coefficient was obtained. This coefficient was calculated by summing the product of the individual correlation coefficients and their respective number of data points; this total was then divided by the total number of data points. In mathematical terms, this formula is expressed as $\Sigma(Nr)/\Sigma'N$. This approach enabled the average correlation coefficient to be obtained from the 10 experimental runs and allowed for the various size of samples. The statistical probability of the association between the two parameters being due to chance wes then calculated, using all the data. For example, 86 simultaneous observations of dP/dt max and dQ/dt max, obtained from 9 dogs, had a mean (weighted) correlation coefficient of 0.7845 (see Table I). The possibility of obtaining this degree of correlation by chance is less than 0.0005.

Attempts to secure a common regression coefficient by pooling all the data gave bizarre results. Thus, when dQ/dt max was compared with dV/dt max, all but one dog showed a positive association between the two parameters, yet the pooled data gave an apparent negative association that was significant at the 5 to 10 per cent level. Review of the data points showed that there was considerable variation in the magnitude of the parameters according to the different dogs, their size, and breed. Hence pooling the data gave an artificial distortion. In the same example, the weighted mean correlation coefficient was significant at a P value of less than 0.0005, e.g., there was a marked relation between peak acceleration (dQ/dt max) in the upper aorta and acceleration (dV/dt max) in the descending aorta, as could be reasonably expected.

To cross check this statistical approach, the binomial probability of an association between two parameters was also calculated. This method is much less sensitive than the Student "t" test; it merely takes into account that a positive association was found in any one experiment, without regard to the number of data points which were used to calculate the association. Nor does it indicate the strength (or weakness) of the association in any particular animal. Each experiment was treated as though the result was chance, akin to tossing a coin. Despite the lack of sensitivity (averaging about 1/5th as sensitive as the "t" test), the binomial probability calculation confirmed that the results were not due to chance. The level of significance was better than the conventional 1–20 level in all but one set of results (see Table I); the exception occurred when descending aortic acceleration, dV/dt max, was compared with the 1/PEP. The Student "t" tests indicated that the 89 results from 10 dogs showed a borderline statistical level of significance of a positive association between these two parameters, whereas the binomial probability was only 0.25.

The ratio dP/dt max ÷ I.P. (instantaneous developed pressure – or instantaneously observed pressure at the time of dP/dt max minus end-diastolic pressure) was then compared with a number of analogous ratios obtained from other channels, e.g., dQ/dt max ÷ I.Q., dV/dt max ÷ I.V., dV/dt max ÷ V. max, as well as the reciprocal of the Pre-Ejection Period, 1/PEP. It was realized that the method of obtaining I.Q. was prone to error, because, if the blood in the aorta was at constant acceleration until nearly peak flow, the slope of the flow signal (acceleration) remains constant over a wide range of flows. Notwithstanding these difficulties, a strong linear association was found when dP/dt ÷ I.P. was compared with dQ/dt ÷ I.Q., based on 86 observations from nine dogs (see Table II). A similar result was obtained when dP/dt max ÷ I.P. was compared with dQ/dt max ÷ Q. max and with 1/PEP. However, the results were equivocal when dP/dt max ÷ I.P. was compared with the velocity ratios dV/dt ÷ I.V. and dV/dt ÷ V. max.

The alternative non-invasive technique of assessing myocardial contractility is to obtain the reciprocal of the Pre-Ejection Period (1/PEP). Tables II and III show that 1/PEP correlated well with dP/dt max ÷ I.P., dV/dt max ÷ I.V., and dV/dt max ÷ V. max.

The use of the ratio dV/dt max ÷ V. max was based on our previous observation that V. max is negatively related to the total peripheral resistance.[8] There-

TABLE II

	Max dP/dt/I.P. – vs. –									
	Max dQ/dt/I.Q.		Max dV/dt/I.V.		Max dV/dt/Vmax		Max dQ/dt/Qmax		1/PEP	
	n	r	n	r	n	r	n	r	n	r
E1	10	0.850	9	0.588	9	0.778	10	0.611	10	0.893
2	10	0.789	10	0.541	10	0.803	10	0.562	10	0.763
3	10	0.504	10	0.358	10	0.237	10	0.814	10	0.267
4	3	0.814	10	−0.337	10	−0.524	3	−0.899	3	−0.878
5	8	0.929	4	−0.255	4	0.027	8	0.932	9	0.663
7	11	0.370	11	0.322	11	0.109	11	0.182	11	−0.237
8	6	−0.322	11	−0.221	11	−0.232	6	−0.089	6	0.701
9	—	—	8	0.398	8	−0.175	—	—	8	0.188
10	13	0.500	13	0.239	13	0.386	13	0.184	13	0.369
11	15	−0.490	15	−0.015	15	0.065	15	−0.392	15	0.042
Total mean *r		0.4076		0.1706		0.1539		0.2631		0.382
n		86		101		101		86		95
t		3.992		1.722		1.547		2.529		3.927
p		0.0005		0.05		0.05–0.1		0.01		0.005

*Weighted mean correlation coefficient.

Individual correlation coefficients, and *weighted mean correlation coefficients and their statistical significance.

TABLE III

	1/PEP - vs. -			
	Max dV/dt/I.V.		Max dV/dt/V. Max	
	n	r	n	r
E1	9	0.698	9	0.732
2	10	0.349	10	0.495
3	10	0.803	10	0.717
4	3	0.329	3	0.532
5	4	−0.862	4	−0.606
7	11	0.092	11	0.280
8	6	−0.430	6	−0.492
9	8	0.838	8	0.701
10	13	−0.527	13	−0.222
11	15	0.626	15	0.701
Total	89		89	
r*		0.2586		0.3510
r		2.525		3.4963
p		0.01		0.0005

Individual correlation coefficients, and *weighted mean correlation coefficients and their statistical significance.

fore, if the peripheral resistance is raised, V. max is low and the ratio dV/dt max ÷ V. max increases. This finding implies that dV/dt max is affected by afterload. Similarly the arterial pressure rises, which, through the various aortic baroceptor reflexes, would be expected to increase contractility.

Table IV summarizes the results when all the ratio indices of myocardial contractility are compared to each other. In all cases the results are from 9 to 10 experimental runs. The weighted mean correlation coefficients are shown together

TABLE IV

dQ/dt/IQ	n	86			
	r	0.4076			
	t	3.9924			
	p	0.0005			
dQ/dt/Q max	n	86			
	r	0.263			
	t	2.524			
	p	0.01			
1/PEP	n	95	86	86	
	r	0.382	0.468	0.440	
	t	3.927	4.853	4.488	
	p	0.005	0.0005	0.0005	
dV/dt/IV	n	101	80	80	89
	r	0.170	0.388	0.253	0.259
	t	1.722	3.719	2.311	2.525
	p	0.05	0.0005	0.0125	0.0125
dV/dt/V max	n	101	80	80	89
	r	0.154	0.502	0.466	0.351
	t	1.547	5.122	4.647	3.496
	p	0.1–0.05	0.0005	0.005	0.0005
		dP/dt/IP	dQ/dt/IQ	dQ/dt/Q max	1/PEP

The weighted mean correlation coefficients resulting when one ratio used as a measure of myocardial contractility is compared with another ratio. All these ratios are in 1/time units. The velocity ratio dV/dt ÷ V max compares reasonably well with the other indices of myocardial contractility.

with their level of statistical significance. It will be seen that the ratio of dV/dt max ÷ I.V. agrees well with the majority of the other ratios, but, when maximum acceleration is divided by peak velocity (dV/dt max ÷ V. max), there is even better agreement.

DISCUSSION

Considerable controversy exists over the definition and quantification of myocardial contractility. Thus Sarnoff and Mitchell[11] state "When from any given end-diastolic pressure or fibre length the ventricle performs more external stroke work, an increase in ventricular contractility is said to have taken place." This explanation implies a relative change without describing in relation to what factor(s). Rusy[12] puts the situation more succinctly, "There are probably a number of indices which at the best only correlate with myocardial contractility. Hence, it is not surprising that different indices are affected differently." Taylor[13] has stated that "none of the indices of myocardial contractility are adequate for several clinical conditions in which knowledge of the state of contractility would be valuable."

Much of the controversy has been based on the assumption that Hill's[14] model of somatic muscle consisting of two elements in series – a contractile element and an elastic element – is transferable to heart muscle. The shortening velocity of this contractile element has been found by Ross *et al.*[15] and Taylor *et al.*[16] to approximate to the ratio dP/dt ÷ I.P. The need for ratios is also implicit in the observations of Kullhardt *et al.*[17] who found that flow acceleration (using dQ/dt max) may, as with dP/dt, be affected by pre-load and afterload. In view of these variations, and without a quantitative expression of myocardial contractility, it is necessary when postulating another potential index to cross compare the postulant with established indices.

In this study, dV/dt max, or peak acceleration of blood in the descending aorta, was found to correlate well with the other rates of change, and the ratio dV/dt max ÷ V. max correlated reasonably well with the ratio dP/dt ÷ I.P. The findings would indicate that, whatever index is the nearest to the true level of myocardial contractility (whatever that may be), the ultrasonic Doppler-shifted velocity probe is capable of giving a reasonable approximation. So caution is perhaps necessary in that the variability of the dV/dt ÷ V. max ratio suggests that some kind of tracking approach, e.g., Trigg's technique[18] in which persistent changes are emphasized, is perhaps desirable. Nevertheless, the advantages of the Doppler oesophageal probe are reasonably self-evident; it is relatively non-invasive in that the probe sits inside the oesophageal tube, and the degree of assault on the patient required to position the probe is not more than that of a naso-gastric tube. This approach is therefore more suitable for clinical use, in contrast to the surgery required for dP/dt max ÷ I.P., dQ/dt ÷ I.Q., etc.

The use of the ratio dV/dt max ÷ V. max has the very practical advantage of obviating the need for calibration, which is the major disadvantage of ultrasonic techniques of circulatory investigation that rely on the Doppler-shift effect. The electronic circuitry required to divide the differentiated signal by the peak velocity signal is not difficult to construct, and a simple meter output of the results of such analogue division is easily feasible. Such a simple black-box approach would provide the anaesthetist with a qualitative index of the state of myocardial contractility.

The alternative non-invasive technique for obtaining an index of myocardial contractility is the use of the Pre-Ejection Period. In our investigation, this parameter was obtained from invasively produced signals as a matter of technical expediency. Blackburn *et al.*[19] have shown that this parameter can be measured by non-invasive means. However, to obtain the P.E.P. non-invasively requires three channels of information, the E.C.G., a phonocardiogram, and some means of identifying the duration of aortic flow, e.g., a carotid pulse sensor. The technical complexities are increased considerably. In contrast, to obtain dV/dt max ÷ V. max requires only one channel of information and has the added advantage that other parts of the velocity signal are also useful, e.g., the ratio of the diastolic to total wave area which is related to the peripheral resistance. Additionally, the complexity of circuitry to produce a moment-to-moment read out is considerably less for the dV/dt max ÷ V. max than for l/PEP.

SUMMARY

An investigation was carried out in dogs to determine how the acceleration of blood in the aorta (dV/dt), as a new index of myocardial contractility compared with existing indices and how they correlated with each other. It was found that the indices derived from velocity and flow of blood, dV/dt max and dQ/dt max, and from intraventricular pressure, dP/dt max, correlate well with each other but there is less agreement between them and the reciprocal of the Pre-Ejection Period, l/PEP. The ratio dP/dt max ÷ I.P. correlated well with dQ/dt max ÷ I.Q. and dQ/dt max ÷ Q. max but not so well with dV/dt max ÷ I.V. (instantaneous velocity) or dV/dt max ÷ V. max and the ratios dQ/dt ÷ I.Q. and dQ/dt ÷ Q max as well as l/PEP. In view of the lack of agreement of quantitative definition of myocardial contractility, the ratio dV/dt ÷ V. max would have several practical advantages as an indicator of the inotropic state of the heart; these are that the probe used to establish descending aortic blood velocity does not require calibration, and the signal can be obtained by a relatively non-invasive technique that is suitable for patient care and yet agrees with other established indices of myocardial contractility.

RÉSUMÉ

Ce travail, effectué chez le chien, avait pour but de comparer entre eux différents indices de contractilité myocardique et, en particulier d'étudier leurs corrélations entre eux et un nouvel index, à savoir, le dV/dt (accélération du flot sanguin aortique). Nos résultats ont montré une bonne corrélation entre les indices dérivés de la vélocité et du débit sanguin (dV/dt max et dQ/dt max) et le dP/dt max dérivé de la pression intraventriculaire; il y avait cependant moins bonne corrélation entre eux et la réciproque de l'intervalle pré-éjection (Pre-Ejection period) – l/PEP.

Le rapport dQ/dt max ÷ I.P. montrait une bonne corrélation avec dQ/dt

max ÷ Q, mais ce n'était pas le cas si on le comparait à dV/dt max ÷ I.V. (vélocité instantanée), à dV/dt max ÷ V. max, à dQ/dt ÷ I.Q., à dQ/dt max ÷ Q max et à 1/PEP.

Considérant qu'il n'y a pas unanimité sur la définition quantitative de la contractilité myocardique, le rapport dV/dt ÷ V max nous semble présenter plusieurs avantages pratiques comme indice de l'état inotropique du coeur, à savoir que (1) le cathéter introduit dans l'œsophage pour délimiter la vélocité du flot sanguin aortique au moyen d'ultrasons ne requiert pas de calibration, (2) que cette technique est relativement non-invasive et (3) qu'il y a bonne corrélation entre elle et les index établis de contractilité myocardique.

APPENDIX I

The requirement for the accurate recording of dP/dt max is that the system should reach 95 per cent of the final value in the time of one cycle that is, in turn, 20 times the basic frequency of the system. For heart rates of 150 beats per minute, or 2.5 per second, the 95 per cent amplitude frequency response should be not less than 50 Hz. To test this requirement for the two cannulae used in this investigation, a pressurized water balloon was attached to each cannula and transducer system and then burst. The resultant oscillations in pressure were recorded on a Tectronix oscilloscope and photographed. The time constant of the rate of decay of the pressure oscillations, damping ratio, damped frequency and natural frequency could then be calculated[10] and from these the rise time and size of the first overshoot could be determined.

The performance specifications for the cannulae used were:

	Cannula 1	*Cannula 2*
Rise Time	0.00141 secs	0.000882 secs
Magnitude of the first overshoot	80%	70%
Damping ratio	0.0718	0.0849
Damped frequency	354	566
Natural frequency	355Hz	568Hz
95 per cent amplitude frequency	54Hz	78Hz

The second cannula was more rigid, and slightly shorter than the first cannula. If the oscillations are tolerable, an under-damped system is the faster acting one.[20] In the system used, the oscillations were tolerable and settled quickly enough to reach the specifications required.

APPENDIX II

The weighted mean correlation coefficient was taken from the expression

sec (1)
$$\bar{r} = \frac{\sum_{1}^{k} (n_j r_j)}{\sum_{1}^{k} (n_j)}$$

An alternative procedure would involve a somewhat elaborate approach to derive the common correlation coefficient using Fisher's 2 Transformation.[21] This transformation is necessary since the distribution of "r" does not follow a normal distribution but follows a rectangulr hyperbole. Hence, it follows that high values of "r" are discriminated against in obtaining the mean unless the "r" values are normalized according to the expression

sec (2)
$$Z = tang^{-1} = 1/2 \log_e \left(\frac{1+r}{1-r}\right) \quad \text{(hyperbolic tangent)}$$

where "r" is the correlation coefficient derived from each experiment.

The mean $\bar{Z}$ is then obtained from

sec (3)
$$\bar{Z} = \frac{\sum_{1}^{k} (n_i - 3)2_i}{\sum_{1}^{k} (n_i - 3)}$$

The common correlation coefficient is then obtained from the expression

sec (4)
$$\bar{r} = \tanh\,(\bar{Z} - a \tanh \bar{Z})$$

where
$$a = \frac{{}^{k}_{1}\,\frac{n_i - 3}{n_i - 1}}{\overset{k}{\underset{1}{2}}\,(n_i - 3)}$$

Student "t" is then obtained from this common correlation coefficient in the usual way. Tables for deriving Z from "r" and $\bar{r}$ from tanh values are available in Geigy.[22]

This transformation was done for all the correlations listed in Tables I to IV, and the common correlation coefficients that emerged differed very little from the weighted mean correlation coefficients although they were all marginally improved at the second or sometimes only the third decimal place of the "r" values. In no case was the level of probability changed. The weighted mean correlation coefficient was preferred because, in deriving the common correlation coefficient, some data were discarded, e.g., all data from any dog for which only three paired data points existed in these particular experimental runs. This procedure reduced the number of dogs on which the first conclusions were based (e.g., that changes in parameter A are associated with changes in parameter B albeit the magnitude of the change varied with different dogs) and, therefore, slightly reduced the level of confidence on which one could base the generalization contained in the conclusions.

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