The Effects of Peripheral Impedance and Inotropic State on the Power Output of the Left Ventricle in Dogs

H. Phoebe Sdougos, Donald L. Schultz, Lip-Bun Tan, Derek H. Bergel, Bheesma Rajagopalan, and Grant de J. Lee

SUMMARY The power output of the left ventricle as measured by the product of the Fourier components of aortic pressure and aortic flow is linked by definition to the arterial impedance facing the heart as measured by the quotient of these components. Consequently, the use of power measurements to assess ventricular performance can be ambiguous when accompanied by afterload changes. The heart is considered to function normally between two extremes, a constant flow pump, and a constant pressure pump, and two power limits are defined from these. The power limits describe the extent to which impedance changes can affect the power delivered by the left ventricle. Measured power changes that are found to lie outside the two limits can be unambiguously ascribed to changes in inotropic state. The results from preliminary dog experiments designed to test this method are reported. Cardiac sympathetic stimulation and isoprenaline infusion were used to provide a pure inotropic stimulus and a mixture of inotropic and afterload changes, respectively. The technique was able to detect inotropic changes in the heart even in the presence of simultaneous changes in afterload. Eight conventional indices of cardiac performance were monitored for comparison. The extent of their afterload dependence may not be as easily quantified. Circ Res 50: 74-85, 1982
Theoretical Analysis

Physiological Considerations

The power delivered by a pump may be calculated from the product of a pressure and flow. From the point of view of the delivery network the pump itself can be regarded as a "black box" which is a source of power, i.e. (pressure × flow). Seen from the point of view of the pump, however, the delivery network is characterized by an input impedance, i.e. (pressure/flow). Thus knowledge of either pressure or flow and impedance enables one to calculate the power output. The interface between the pump and the load—identified by the two variables, power and impedance—is of prime importance, since power transfer from the pump to the load depends on correct matching of the two systems.

In the case of the heart, the pump consists of the whole heart up to and including the aortic valve. Thus power must be calculated as the product of the aortic pressure and aortic flow, measured at the same site (Bergel et al., 1970). It is apparent that power is linked directly to the load impedance. Thus if power is to be used to characterize the inotropic state of the heart, it must be possible to separate the two components, inotropic state of the ventricle and afterload of the systemic circulation.

The method may be illustrated by considering pressure-flow relationships of the dog left ventricle from the literature (Sagawa, 1967; Herndon and Sagawa, 1969) which are presented in Figure 1. Each curve represents the cardiac output of the left ventricle as a function of mean aortic pressure with constant left atrial pressure and inotropic state. The pressure scale has been normalized to the maximum ejection pressure attained at each filling state, and this pressure increases with increasing left atrial pressure. At lower aortic pressures, the flow curve approximates to the horizontal interrupted lines, indicating that flow is not affected much by load and the ventricle functions as a constant flow source.

The alternative behavior of a constant pressure source would be indicated by a vertical line, and this type of behavior is approached as the load is raised. It will be seen that, with increasing, yet still normal, left atrial pressure, the constant pressure source approximation improves. Thus for any value of mean left atrial pressure, the two interrupted lines, together with the axes, enclose a rectangle (e.g., P_C and Q_C for the highest left atrial pressure in Fig. 1). Since a real pump must behave as something between a constant pressure and a constant flow source, all measurements on a left ventricle at fixed filling and inotropic state must be found to lie somewhere within such a rectangle. If one measures a single value, P' and Q', in the resting state, the limits to performance in the future would be those of constant flow Q' at any pressure P, and constant pressure P' at any flow Q, but performance above and below these criteria can be taken to represent a change in filling or inotropic state as defined here. Only if filling state and/or inotropic state alter can the curve change to conform to a new pair of limits (e.g., P_C, Q_C).

Power Limits

The concept of two limits of constant pressure and constant flow allows the development of a
FIGURE 2 Nomogram to illustrate the derivation of the two power limits. $P_i$, $Q_i$, $Z_i$, and $W_i$ represent the initial mean values of aortic pressure, aortic flow, impedance (resistance) and power. $Z_2$ is the mean impedance of the perturbed state. $P'$ is the pressure for a constant flow pump giving a power output of $W_Q$, and $Q'$ is the flow for a constant pressure pump giving a power output of $W_P$.

Two power limits have thus been obtained representing the maximum extent to which impedance changes can affect the power delivered by the left ventricle. The operating point of the cardiovascular system may be perturbed by inotropic intervention or afterload changes, or both. The new power level may then be calculated and compared to that of the original state. If the power level of the perturbed state is found to lie between the limits $W_P$ and $W_Q$ then, no matter what the perturbation, that same power level could have equally well been attained by a simple change of impedance. However, if the power level of the perturbed state is found to lie outside the limits of $W_P$ and $W_Q$, then the perturbation can unambiguously be ascribed to an inotropic effect.

Harmonic Analysis

Important information may be lost if only mean values of pressure and flow are measured, so complete time-varying waveforms have been analyzed. In order to obtain values for power and impedance, it is necessary to be able to operate mathematically on these waveforms. Since they are nearly periodic, they may be represented by Fourier series (Attinger et al., 1966). Power and impedance are then evaluated in terms of Fourier harmonics with the assumption that the overall system is linear. The validity of this assumption has been examined by several authors (Attinger et al., 1966; Dick et al., 1968) who have found the arterial system to be very nearly linear.

The aortic pressure and flow waveforms may be expressed as the Fourier series

$$P(t) = P_0 + \sum_{n=1}^{\infty} P_n \cos(n\omega t - \phi_n)$$

$$Q(t) = Q_0 + \sum_{m=1}^{\infty} Q_m \cos(m\omega t - \theta_m).$$

The cycle average power may then be calculated from the product of the two series:

$$W = \frac{1}{T} \int_0^T W(t)dt = \frac{1}{T} \int_0^T P(t) \cdot Q(t)dt$$

where, $T = 2\pi/\omega$. The second order terms associated with the kinetic energy of the ejected fluid are neglected since, when measured, they were found to be small in all cases. The cycle average power finally reduces to a harmonic series (see Appendix):

$$W = P_0Q_0 + \frac{1}{2} \sum_{n=1}^{\infty} P_nQ_n \cos(\phi_n - \theta_n)$$

Each term in this series represents the power delivered at each harmonic, the fundamental frequency ($f = 1/T$) being the heart rate.

Aortic input impedance terms are also obtained at each harmonic. Although impedance is, in gen-
eral, a complex function, only its real part plays an energy-dissipating role (O’Rourke and Taylor, 1967). At any harmonic, this component may be expressed as

\[ Z_n = \frac{P_n}{Q_n} \cos(\theta_n - \phi_n) \]  

(3)

Just as the cycle average power is evaluated in terms of the Fourier components obtained from the pressure and flow waveforms, so are the two power limits, \( W_p \) and \( W_q \).

\[ W_{np} = W_{n1} \frac{Z_{n1}}{Z_{n2}} \quad \text{and} \quad W_{nq} = W_{n1} \frac{Z_{n2}}{Z_{n1}} \]  

(4)

where \( W_{n1} \) and \( Z_{n1} \) are the harmonic components of power and impedance (Eqs. 2 and 3) at the original resting state, and \( Z_{n2} \) is the harmonic component of impedance at the perturbed state.

A diagram corresponding to Figure 2 may now be drawn for each harmonic component. For example, considering the zeroth, first, and second harmonics at a resting basal level followed by one perturbed level, the nomogram in Figure 2 would become the three-dimensional sketch in Figure 3. The representation here is purely schematic; consequently, the logarithmic scale originally used in Figure 2 has been replaced by a linear scale.

Accurate impedance measurements are difficult to make. They are subject to the influences introduced by many reflection sites in the aorta, as well as the mathematical errors created when the quotient is taken of two experimentally determined parameters such as pressure and flow, which are themselves subject to measurement errors. As a result, it is not unusual to find that there is noise in an impedance spectrum. Furthermore, the level of this noise is amplified if the ratio of two impedances is to be evaluated, as the case for the definition of the two power limits (Eq. 4). A simple way of reducing this noise is to define an effective impedance. This may be done by calculating a mean impedance from the first nine harmonics (excluding the zeroth). The power limits would then reduce to

\[ W_{np} = W_{n1} \frac{Z_1}{Z_2} \quad \text{and} \quad W_{nq} = W_{n1} \frac{Z_2}{Z_1} \]  

(5)

where \( Z_1 \) and \( Z_2 \) are the effective impedances at intervention levels 1 and 2.

Using the definition of the two power limits (Eq. 5), their difference at any harmonic becomes

\[ W_{np} - W_{nq} = W_{n1} \left( \frac{Z_1}{Z_2} - \frac{Z_2}{Z_1} \right) = W_{n1} \left( \frac{Z_1^2 - Z_2^2}{Z_1 Z_2} \right) \]

which reduces to

\[ W_{np} - W_{nq} = W_{n1} \left( 1 + \frac{Z_2}{Z_1} \right) \left( \frac{Z_1}{Z_2} - 1 \right) \]

Substituting \( Z_2 = Z_1 + \Delta Z \), where \( \Delta Z \) is the change in the effective impedance, the expression finally reduces to

\[ |W_{np} - W_{nq}| \approx 2 \cdot W_{n1} \cdot \frac{\Delta Z}{Z_1}. \]  

(6)

The magnitude of the difference between the two power limits at any harmonic depends on the magnitude of the absolute power term at the previous intervention level and on the percentage change in the impedance term form one intervention level to the other.

This concept was developed with a view to clinical application and in what follows we describe a series of animal measurements designed to test the method.

Methods

General Preparation

Measurements were made on five adult mongrel dogs of average weight 23 kg. After premedication with Themalon (diethylthiambutene hydrochloride, Burroughs Wellcome: 1 mg/kg, im) anesthesia was induced with chloralose (128 mg/kg) and urethane (640 mg/kg) given intravenously as a solution.
in a 50:50 mixture of 0.9% saline and polyethylene glycol (B.D.H.) at a dose of 2 ml/kg. After a midline thoracotomy, respiration was maintained with a Starling ventilator, the end-expiratory pressure being held at 5 cm H₂O, using oxygen-enriched air. Arterial blood gases were monitored at regular intervals and adjusted by manipulation of the respiratory tidal volume and the use of intravenous sodium bicarbonate. The readings were kept within the following ranges:

\[ \text{PO}_2 > 80 \text{ mm Hg}; \text{pH} \sim 7.25 - 7.35; \]
\[ \text{PCO}_2 \sim 35 - 45 \text{ mm Hg} \]

The aortic root was cleared for the attachment of an electromagnetic flow cuff (S.E. Laboratories), and pressure in the ascending aorta was measured with a Millar catheter-tip manometer that had been inserted via a femoral artery. Pressure was also monitored inside the left ventricle, where either a Konigsberg microanometer or a second Millar catheter-tip manometer was placed through an apical stab wound. An S.E. type 425 electromagnetic flowmeter was used to measure the flow and S.E. type 4000 amplifiers were used for both the pressure signals. All data, including an ECG and a voice commentary, were recorded onto an Ampex SP 300 tape recorder operating in the FM mode with a bandwidth of 3 kHz.

Cardiac Sympathetic Stimulation

Measurements were made under control conditions and during graded cardiac sympathetic stimulation. The latter was performed by electrical stimulation of the left sympathetic chain (Furnival et al., 1973). The chain was identified at the neck of the second rib and placed in a cuff containing a pair of platinum electrodes. Square wave pulses of 10-V intensity and 10-msec duration were used at frequencies between 1 and 5 Hz. Stimulation was continued for a period of 10 seconds, at which time a steady state was attained. All measurements were made in the 10-second interval after stimulation had been stopped to obviate the problem of stimulus-derived noise in the flow record.

Isoprenaline Infusion

When the animals were considered to be in a stable resting state, an intravenous infusion of isoprenaline was started, using a Harvard syringe pump. A range of infusion rates from 0.25 to 6.0 µg/min was selected, the starting infusion always being at the weaker end of the scale. The infusion was held at each level for 6 minutes so that a steady state response was attained. The infusion rate was then increased if no untoward effects had been observed.

Data Processing

Appropriate sections of data were digitized on a DEC PDP 11-34 computer by means of an AR 11 A/D converter and stored on RK05 discs. A sampling interval of 2 msec (500 Hz) was used in all cases. This frequency is well above the highest frequency contained in cardiovascular waveforms as predicted by several authors (Patel et al., 1965; McDonald, 1974).

Ten complete cycles were selected to represent each level of intervention, including control conditions. The beginning and end of each cycle were defined by the R wave in the QRS complex of the ECG. For the control (resting) data, the 10 cycles were selected to be in a region of peak inspiration. In the case of sympathetic stimulation, cycles were chosen from the first 10-second period immediately after stimulation, where the cardiac response was at a steady state. For the isoprenaline infusion, cycles were selected from a region of peak inspiration after the 5th minute of infusion at each level. After the initial cycle-selection process, all further data manipulation and analysis was performed on a DEC PDP 11-45 computer operating on an IAS time-sharing system.

Each of the pressure and flow waveforms was Fourier analyzed and the information at each harmonic stored in terms of a modulus and a phase angle. The flow data were corrected to take into account the frequency response of the flowmeter (Gessner and Bergel, 1964). No corrections were made to the pressure data, since both the Millar and Konigsberg transducers have a frequency response that is flat to over 500 Hz. Henceforth, most analyses were performed in terms of individual harmonics, although it was still possible to deal with the intact waveforms as well. For example, Figure 4, A and B, shows the results of plotting (A) 10 individual aortic flow waveforms together and (B) 10 individual aortic pressure waveforms. The results of Fourier analysis of the average of these 10 individual waveforms are also shown in each figure in terms of the moduli at each harmonic.

Using information from the Fourier analysis of 10 individual aortic flow and aortic pressure waveforms, power information may be obtained in terms of a mean value at each harmonic (Eq. 2) and one standard deviation about that mean value. It is, however, important to note that no such statistical information may be obtained for the two power limits \( W_P \) and \( W_Q \). The reason for this becomes apparent when the definitions of the power limits (Eq. 5) are considered. The power limits for any level of intervention are evaluated as the product of the power term at the preceding level and the ratio of two impedance terms, one at the same intervention level as the power term and one at the subsequent intervention level. It would be meaningless to try to combine individual cycles in any way, since the statistical information so obtained would depend solely on which combination of power and impedance was chosen.
POWER OUTPUT IN DOGS: IMPEDANCE & INOTROPIC EFFECTS/Sdougos et al.

Cardiac Sympathetic Stimulation

Cardiac sympathetic stimulation was performed on three of the five animals studied. A total of six experiments was performed, two on each dog. When the preliminary dissections were completed and blood gases were stable, these animals had an average blood pressure of 111.5 ± 11.2 mm Hg, heart rate 164 ± 18 beats/min, and cardiac output 1.94 ± 0.55 liter/min. Their average mean impedance (resistance) was 4.98 X 10^8 ± 1.51 x 10^8 N-sec/m^5, peak power output was 2.94 ± 0.63 W, and (dPLV/dt)max 2565 ± 432 mm Hg/sec.

The results of cardiac sympathetic stimulation on a group of eight indices of myocardial performance are shown in Figure 5. The values for each experiment have been normalized with the basal resting state for that particular experiment. A linear regression has been performed with the stimulation frequency as the independent variable, and the correlation coefficient (r) is given for each case. There was no significant change in either heart rate or mean aortic pressure as a result of the sympathetic stimulation.

Figures 6A, B, and C, show the relationship between the Fourier components of the power waveform and the two power limits, Wp and W0, for data obtained from three experiments. Each of these figures is the two-dimensional simplification of the format presented in Figure 3, and shows components of power plotted for the zeroth, first, second, and third harmonics. The stimulation rate of the sympathetic chain is indicated non-linearly on the abscissa. The basal resting state is also plotted. Each point is an average value derived from the Fourier components obtained from 10 individual pairs of aortic flow and aortic pressure waveforms as previously described. Error bars are plotted in each case at one standard deviation. The two power limits, Wp and W0, are also plotted at each harmonic. No statistical information may be plotted for the power limits since none is defined (see Data Processing).

The complete power waveforms for the case described in Figure 6C are shown in Figure 7A.

In the interests of brevity, Figure 6 shows data from only three of the six experiments performed. The results from all six experiments may be summarized in terms of the percentage of the power values lying outside and above the two power limits for each harmonic. For the zeroth harmonic, 50% of the mean power values were outside and above the limits, 79% for the first harmonic, 93% for the second harmonic, and 100% for the third harmonic.

Linear regressions were also performed on the first four harmonics of power and impedance. Based on these regression lines, a percentage change from the response at the basal resting level to the peak response at the highest stimulation rate (5 Hz) has been calculated. This percentage is shown in Table 1A.

Isoprenaline Infusion

All five of the dogs studied were given isoprenaline infusions. At the resting pre-isoprenaline level,
The relationship between the Fourier components of the power waveform and the two power limits is shown for two separate experiments in Figure 9, A and B. The isoprenaline infusion rate is plotted along the abscissa. The complete power waveforms for the case described in Figure 9B are shown in Figure 7B.

A total of nine separate infusions of isoprenaline were given to the five animals. Again, in the interests of brevity, Figure 9 shows data from only two of the nine infusions. As for the cardiac sympathetic stimulation, the results from all nine isoprenaline infusion experiments may be summarized in terms of the percentage of the power values lying outside and above the two power limits for each harmonic. For the zeroth harmonic, 20% of the mean power values were outside and above the limits, 90% for the first harmonic, 75% for the second harmonic, and 85% for the third harmonic.

Linear regressions were performed on the first four harmonics of power and impedance. Based on these regression lines, the percentage change from

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**Figure 5** Effects of cardiac sympathetic stimulation on a group of eight conventional indices of myocardial performance. Linear regressions on the stimulation frequency gave the following correlation coefficients: cardiac output 0.72; dP/dt\(_{\text{max}}\) 0.89; dV/dt\(_{\text{max}}\) 0.75; pre-ejection period -0.82; average ejection power 0.87; peak power 0.87; stroke work 0.79; dP/dt\(_{\text{min}}\) -0.81.

they had an average blood pressure of 121.9 ± 12.3 mm Hg, heart rate 148 ± 26 beats/min, and cardiac output 1.88 ± 0.27 liters/min. Their average mean impedance was 5.39 × 10\(^8\) ± 1.15 × 10\(^8\) N-sec/m\(^2\), peak power output 3.17 ± 0.39 watts, and (dP\(_{LV}/dt\)\(_{\text{max}}\)) \(_{\text{max}}\) 2855 ± 470 mm Hg.

The results of an infusion of isoprenaline on the same group of eight indices of myocardial performance are shown in Figure 8. As with the cardiac sympathetic stimulation, the values for each experiment have been normalized with the basal resting state for that particular experiment. Again, the appropriate linear regression correlation coefficients (r) have been calculated and are given for each case. It should be noted here that these coefficients are lower than those obtained for cardiac sympathetic stimulation. Both the heart rate and the mean aortic pressure changed by approximately 25% at the highest infusion rate as compared to the resting state.

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**Figure 6** Relations between the Fourier components of the power waveform and the two power limits for three separate cardiac sympathetic stimulation experiments. Components of power are plotted for the zeroth (top), first, second, and third harmonics. The stimulation rate is plotted along the abscissa.
Power Output in Dogs: Impedance & Inotropic Effects

Discussion

Cardiac Sympathetic Stimulation

Stimulation of the left sympathetic chain is a simple way of providing a large inotropic increase with little change in heart rate (Furnival et al., 1973). Consequently, it is an intervention that may easily be detected by significant changes in a wide range of indices of myocardial performance. Eight such indices are presented in Figure 6C. They all show a good linear relationship to the stimulation rate, with correlation coefficients ranging from 0.72 to 0.89. The resulting changes in myocardial performance are quite substantial with relative ratio changes between the peak stimulation and the resting states ranging from 1.4 to 1.6 for cardiac output, stroke work, and (dP/dt)min, and from 2.1 to 2.8 for the remaining indices. Such changes are also reflected in the complete power waveforms. Figure 7A represents the power waveforms for the case shown in Figure 6C. The peak power is seen to rise with each step in the stimulation rate. At the same time, the onset of the ejection comes progressively earlier in the cycle and there is an increase in the maximum rate of change of power in this region.

All these factors would tend to suggest that the heart is responding to the sympathetic stimulation by an increase in inotropic state. However, such a judgement based solely on the above criteria would be ambiguous since, as yet, no attention has been paid to the effects, if any, of afterload (impedance) changes. This must be done, since all power and work criteria are linked to afterload changes by definition, and other criteria like (dP/dt)max and (dV/dt)max are suspected of being afterload sensitive (Van den Bos et al., 1975).

Before considering afterload changes, the relationship between the Fourier components of the power waveform and the two power limits of a constant pressure and a constant flow pump should be investigated. This relationship may be seen in Figure 6A-C. Only the first four Fourier components of power are plotted. It can be deduced from

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<th>Table 1 Power and Impedence Values and Peak Changes Obtained during (A) Cardiac Stimulation and (B) Isoprenaline Infusion</th>
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<td>1A. Cardiac sympathetic stimulation</td>
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\( W_n \) and \( W_p \) are the power values at the basal resting state and at the peak intervention, respectively. \( Z_n \) and \( Z_p \) are the corresponding impedance values. \( n \) is the harmonic number.
Effects of isoprenaline infusion on a group of eight conventional indices of myocardial performance. Linear regressions on infusion rate gave the following correlation coefficients: cardiac output 0.69; $dP/dt_{\text{max}}$ 0.43; $dV/dt_{\text{max}}$ 0.71; pre-ejection period $-0.75$; average ejection power 0.25; peak power 0.58; stroke work 0.17; $dP/dt_{\text{min}}$ $-0.28$.

The scale of the ordinate that the magnitude of the power decreases steadily with increasing harmonics. On the average, over all the experiments, the power value at the third harmonic was found to be of the order of 1%, or less, of the corresponding mean value (zeroth harmonic). For the present purpose, the power information contained beyond the third harmonic is considered to be insignificant.

Detailed inspection of any one of A-C, Figure 6, brings out the major points of interest. In Figure 6C are plotted the first four harmonics of the power waveforms resulting from a graded stimulation of the sympathetic chain at 1, 2, and 4 Hz. The basal resting level prior to the start of the stimulation is also plotted. The two power limits, $W_P$ and $W_Q$, are shown at each harmonic, the separation between the two levels being denoted by the spread between the two sloping lines. The definition of the two power limits (Eq. 5) involves events that have taken place at two separate times. For their evaluation at any time, it is necessary to know the impedance at that stage, together with the power and the impedance at the stage directly preceding it. Thus, no power limits can be derived for the basal control level since nothing came before it.

Alternatively, the definition of the two power limits may be considered as the product of two terms, a power term and an impedance ratio term. Consequently, the spread between the two limits is a direct indication of the change in impedance from one level of intervention to the next. With cardiac sympathetic stimulation, impedance changes are expected to be small, since the stimulation has a predominantly inotropic effect (Table 1A). This was indeed found to be the case for all the harmonic terms (excluding the zeroth) shown in Figure 6, A-C. For the stimulation in Figure 6, A and B, the power limits are virtually coincident, and in Figure 6C the greatest separation, occurring at the first harmonic.

Relationship between the Fourier components of the power waveform and the two power limits for two isoprenaline infusion experiments. Components of power are plotted for the zeroth (top), first, second, and third harmonics. The infusion rate is plotted along the abscissa.
The spread between the power limits is considerably greater for the zeroth harmonic; so much so that at 1 and 2 Hz in Figure 6C, the actual power value falls just inside the two limits. The difference between the zeroth harmonic and the first three harmonics is due to the differences in the actual magnitudes of the power terms at each harmonic and the percentage change in the impedance terms. This may be seen from Equation 6 which describes the differences between the two power limits.

At the zeroth harmonic, therefore, the spread between the power limits is greatly influenced by the actual magnitude of the power term \( W_n \). For example, in the data presented in Figure 6C, the ratios of the power term at the zeroth harmonic to the corresponding power term at the first harmonic range from 16 to 27, whereas the power terms at the first, second, and third harmonics are of approximately the same order of magnitude.

Some of the ambiguity occasioned by the afterload dependence of various cardiac indices, particularly those derived from power criteria, is eliminated by a consideration of power values relative to the two power limits when the ventricle is considered as a constant pressure or a constant flow pump. Examination of Figure 6 indicates that at the first, second, and third harmonics of power, the heart is indeed responding to the sympathetic stimulation by an unambiguous increase in inotropic activity. At these harmonics, any possible contribution to the power terms from impedance changes may be excluded. Over all, the cardiac sympathetic stimulation experiments 79%, 93% and 100% of the mean power terms at the first, second, and third harmonics, respectively, were found to lie outside and above their corresponding power limits. This was true of only 50% of the power values at the zeroth harmonic. Consequently, at this harmonic there may still be some ambiguity which can be explained from Equation 6 by the actual magnitudes of the terms concerned (Table 1A).

**Isoprenaline Infusion**

Testing the power limits separation technique with cardiac sympathetic stimulation experiments shows that it is indeed sensitive to changes in the inotropic state of the heart. However, since the afterload changes produced by the stimulation are small, the test is not completely rigorous. For this reason, experiments were performed in which graded infusions of isoprenaline were used to provide both an inotropic stimulus and a marked afterload reduction. The conventional cardiac indices presented in Figure 8 are taken from nine isoprenaline infusion experiments. Compared with Figure 5, group correlation is poor because the more complex effects of isoprenaline elicit differences between individual animals.

Clarification results when all eight indices from one experiment are considered together as in Figure 10. It can be seen that some of the changes induced by the drug in the individual variables may no longer be statistically significant. Furthermore, these changes are not always unidirectional, the magnitudes of the indices sometimes decreasing rather than increasing, and vice versa. Some of the greatest variability is shown by the work and power criteria, yet the complete power waveforms for this particular case, as seen in Figure 7B, still conform to the overall pattern established with cardiac sympathetic stimulation in Figure 7A. The peak power rises with increasing infusion rate, and the onset of contraction comes progressively earlier with corresponding increases in the maximum rate of change of power during contraction.

Over and above the inotropic stimulus that is common to the experiments described in Figures 6 and 9, there are marked afterload changes in the

**FIGURE 10 Effects of isoprenaline infusion on a group of eight conventional indices of myocardial performance. Data are plotted from one single experiment, results from which are also shown in Figures 7B and 9B. The points are mean values obtained by considering 10 individual aortic flow and pressure waveforms. The error bars are plotted at one standard deviation.**
latter group (Table 1B). Yet the general appearance of the Fourier components of power and the corresponding power limits presented in Figure 9 is very similar to that of Figure 6. The most significant aspect is that at the first, second, and third harmonics all power values are outside the two power limits. The results for all of the isoprenaline infusion experiments show that 90%, 75%, and 85% of the mean power terms at the first, second, and third harmonics, respectively, were found to lie outside and above their corresponding power limits. Only 20% of the zeroth power values lay outside the power limits when isoprenaline was infused. Thus, the only ambiguity remains at the zeroth harmonic where, because of the magnitude of the power terms and the impedance changes that are involved, the technique is not always able to separate the effects of a change in resistance on the mean power output of the left ventricle.

We conclude that this technique can detect inotropic changes in the heart, even in the presence of simultaneous changes in afterload.

Appendix

Derivation of Harmonic Series for Cycle Average Power

The aortic pressure and flow waveforms may be expressed as the Fourier series:

\[ P(t) = P_0 + \sum_{n=1}^{\infty} P_n \cos(n\omega t - \phi_n) \]
\[ Q(t) = Q_0 + \sum_{m=1}^{\infty} Q_m \cos(m\omega t - \theta_m). \]

The cycle average power is calculated from the product of the two series:

\[ W = \frac{1}{T} \int_0^T W(t) \, dt = \frac{1}{T} \int_0^T P(t) \cdot Q(t) \, dt \]
\[ = P_0 Q_0 + \frac{\omega}{2\pi} \int_0^{2\pi/\omega} \left[ \sum_{n=1}^{\infty} P_n \cos(n\omega t - \phi_n) \right] \cdot \left[ \sum_{m=1}^{\infty} Q_m \cos(m\omega t - \theta_m) \right] \, dt. \]

The individual terms under the summation in the integral may be expressed as:

\[ W_{nm} = \frac{\omega}{2\pi} P_n Q_m \int_0^{2\pi/\omega} \cos(n\omega t - \phi_n) \cdot \cos(m\omega t - \theta_m) \, dt \]
\[ = \frac{\omega}{2\pi} P_n Q_m \int_0^{2\pi/\omega} \frac{1}{2} \cos((n - m)\omega t - (\phi_n - \theta_m)) \, dt \]
\[ = \frac{\omega}{2\pi} P_n Q_m \int_0^{2\pi/\omega} \left[ \frac{1}{2} \cos((n - m)\omega t - (\phi_n + \theta_m)) \right] \, dt. \]

For \( m \neq n \), this reduces to:

\[ W_{nm} = \frac{\omega}{2\pi} P_n Q_m \int_0^{2\pi/\omega} \left[ \frac{1}{2} \cos(2\omega t - (\phi_n + \theta_n)) \right] \, dt \]
\[ = \left[ \frac{1}{2\omega} \sin(2\omega t - (\phi_n + \theta_n)) \right]_0^{2\pi/\omega} = 0, \]

and the cross products are thus zero. For \( m = n \), however:

\[ W_{nn} = \frac{\omega}{2\pi} P_n Q_n \int_0^{2\pi/\omega} \left[ \frac{1}{2} \cos(0 - (\phi_n - \theta_n)) \right] \cdot \cos((2n)\omega t - (\phi_n + \theta_n)) \, dt \]
\[ = \frac{1}{2} \cos(2n\omega t - (\phi_n + \theta_n)) \right]_0^{2\pi/\omega} = 0, \]

i.e., the first term in \( W_{nn} \) is also zero. Thus,

\[ W_{nn} = \frac{\omega}{2\pi} P_n Q_n \int_0^{2\pi/\omega} \frac{1}{2} \cos(\theta_n - \phi_n) \, dt \]
\[ = \frac{P_n Q_n}{2} \cos(\theta_n - \phi_n). \]

The expression for the cycle average power finally becomes:

\[ W = P_0 Q_0 + \frac{1}{2} \sum_{n=1}^{\infty} P_n Q_n \cos(\theta_n - \phi_n). \]

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H P Sdougos, D L Schultz, L B Tan, D H Bergel, B Rajagopalan and G de J Lee

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