DIRECT ASSESSMENT OF CARDIAC FUNCTION

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Measurement of cardiac performance

In the assessment of the effects of drugs on the heart it is important to define the aspects of cardiac function to be measured. We seem to be coming through a period of philosophical revision of our understanding of cardiac function and a new consensus is beginning to appear. The essential part of the heart as far as the systemic circulation is concerned is the left ventricle and most attention is directed to the performance of this chamber and its alteration by disease or drugs.

The basic simplification was to regard the heart as a "black box" capable of generating blood flow at the required aortic pressure, and to measure only these variables. This approach soon gave way to the appreciation of interplay between such factors as pressure, flow and left ventricular volume. An early result of these ideas was the *Frank-Starling hypothesis* which relates left ventricular performance to the initial stretch of the muscle fibres evident as the end-diastolic volume and indirectly (in relation to the mechanical properties of the left ventricular wall in diastole) to the end-diastolic pressure. This concept led to the definition of two pressure variables, the 'pre-load', indicating the distending pressure for the initial stretch of muscle fibres, and the 'after-load' related to the resistance presented to left ventricular ejection. Both these variables are modified by peripheral vascular tone, changes in capacitance vessel tone shifting blood from peripheral venous pools to the central circulation to alter pre-load and changes in resistance vessel tone affecting after-load directly. Modification of these two different aspects of peripheral vascular tone has been utilized in the vasodilator therapy of heart failure. Studies in human disease states are made difficult by the natural increase in sympathetic activity when there is inadequate cardiac performance (Chidsey, Braunwald & Morrow, 1968). Drug responses evident in animal work or in near-normal human subjects may not be directly applicable to the different autonomic background of congestive heart failure.

The concept of a *descending limb* of the Frank-Starling curve has given rise to much difficulty. The idea arose from studies suggesting a fall off in cardiac performance as left ventricular filling pressure (pre-load) rose to abnormally high values. This concept offers a facile explanation of the beneficial effect of diuretic treatment, in that a fall in left ventricular filling pressure might be expected to

increase cardiac output, under these circumstances. Although apparently confirmed in man (Braunwald, 1965) there are many objections to the existence of a descending limb (Guyton, 1963; Noble, 1978) and the original findings may well have been due to technical problems. In human disease a reduction in filling pressure is consistently associated with a fall rather than a rise in cardiac output (Stampfer, Epstein, Beiser & Braunwald, 1968; Bradley, 1977) and the benefits of diuretic therapy and of reduction in pre-load by vasodilators are mainly in the relief of pulmonary congestion secondary to the fall in pulmonary venous pressure.

The data formerly regarded as showing a descending limb of the Frank-Starling curve is probably best interpreted in terms of a change to a different curve among a family of parallel curves associated with different levels of cardiac performance. An improvement in performance in these terms might be expected when a reduction in pre-load by diuretics or vasodilators improves sub-endocardial coronary blood flow by increasing the aorta to left ventricular cavity pressure difference in diastole or prevents functional mitral incompetence as the left ventricular diastolic volume is reduced. Although the base-line for filling pressure cannot be determined, the description of changes in left ventricular performance in terms of cardiac output against filling pressure curves remains a valid exercise. This approach requires the determination of several points on the curve by manipulation of blood volume as shown by Bradley (1977) and is not easily adapted to the study of interventions such as the effect of drugs.

The suggestion, based on studies of skeletal muscle, that left ventricular performance could be analysed into *force and velocity components* (Fry, Griggs & Greenfield, 1964) and that velocity and force would be affected by conventional inotropic interventions and only force by changes in pre-load (Sonnenblick, Glick, Morrow & Braunwald, 1964), has been weakened by the evidence that both responses are fundamentally similar and are mediated by increased sarcoplasmic calcium ion concentration (Noble, 1978). The reciprocal relation between force and velocity as end products of ventricular work led to the use of left ventricular power, the product of force and velocity, as an overall index of left ventricular performance, but

there is suspicion that power may be dependent on load (CIBA Foundation Symposium, 1974), and the combination of the two aspects of left ventricular work is not necessarily an advantage in the assessment of interventions.

The apparent simplicity of left ventricular pressure measurement as an estimate of force is ruined by the appreciation that left ventricular volume measurements are also needed to assess total left ventricular wall force from the Laplace relationship ($F = \pi r^2 P$). As the inotropic effects of drugs might be expected to be manifest in the velocity aspects of contraction much attention has been paid to this variable. Attempts to define a 'true index of contractility' have generally been frustrating (Noble, 1977) and the best approach seems to be the simple measurement of the maximum of the first derivative of the left ventricular pressure (peak dP/dt) which is intuitively related to the velocity of contraction and has the advantage of being free of base-line problems and relatively little affected by other variables. We have used this measurement to detect the reduction in contractility produced by beta-blockade with practolol in the absence of any other major impairment of cardiac performance (Gibson & Coltart, 1972). The high quality technology required for measurement of peak dP/dt is generally available. Perfect left ventricular pressure measurements are required for electrical differentiation and, although a short needle in the left ventricular apex was used originally, the widespread availability of catheter-tip manometers has brought this technique at a price, within the reach of all cardiac catheterization laboratories.

Measurement of cardiac output

The concept that the main function of the heart is to maintain systemic blood flow had led to an almost obsessive concern with cardiac output as an estimate of cardiac performance, almost without regard to the technical difficulties of its measurement (Taylor, 1977).

One of the original products of the introduction of cardiac catheterization was the ability to obtain truly mixed venous blood samples from the pulmonary artery, to allow an estimate of cardiac output (l/min) by the *Fick principle* as oxygen consumption (ml/min) divided by arteriovenous oxygen difference (ml/l). Accurate results required the meticulous analysis of oxygen content of blood samples, usually by the tedious manometric van Slyke technique and the careful collection of expired air over a known interval. These techniques are complex and difficult to maintain at a high standard in a busy laboratory, so that inaccuracies are almost certain to occur. The temptation to simplify the method is very great and often leads to deterioration in the results. Although simpler methods of blood-gas analysis such as the

Lex-O₂-Con seem satisfactory in skilled hands (Adams & Cole, 1975), the realization that the major variable in changes of cardiac output is the mixed venous oxygen saturation has sometimes led to estimation of arterial oxygen content and of oxygen consumption to the detriment of the accuracy of the method. Nevertheless, in spite of its inherent inaccuracy and multiple difficulties, the Fick remains the reference technique for cardiac output measurement.

The *indicator dilution technique* for cardiac output measurement was immediately appealing in its simplicity and repeatability, making it useful to assess interventions, such as the effect of drugs.

In essence when a bolus of indicator is injected into the venous system, the spread of the indicator during its passage through the heart is influenced by the cardiac output, and a detector on the arterial side will record a concentration-time curve which increases in area as the output falls. Similar principles can be applied in limited parts of the circulation such as the right heart (Bradley, 1977) or in the coronary sinus to measure coronary venous flow (Ganz, Tamura, Marcus, Donoso, Yoshida & Swan, 1971).

Technical problems, for instance the elimination of recirculating indicator by an arbitrary logarithmic extrapolation of the first circulation decay slope and the accurate calibration of the *in vivo* concentration of indicator may give rise to problems, but meticulous work can give good agreement with the Fick method (Taylor, 1966).

The usual indicator has been a blue dye making use of recording systems originally introduced to detect unoxygenated haemoglobin in the measurement of oxygen saturation, but a green dye which is detected at a wave length independent of oxygen saturation is useful for measurements within the right heart. Many other indicators have been used; especially useful are indicators that disappear from the circulation after one passage, removing the need for extrapolation to eliminate a recirculation curve. Cold saline which uses temperature change as the indicator can be used in this way with a sensitive thermistor or thermocouple (Bradley, 1977) and lends itself particularly to automatic measurement of curve area, making for rapid repeated measurements especially suitable for drug studies.

Many of the problems of indicator dilution curve calibration are overcome by the dynamic approach originated by Sparling, Mook, Nieveen, van der Sikke & Zijlstra (1960). We have evaluated this method (Emanuel, Hamer, Chiang, Norman & Manders, 1966; Shinebourne, Fleming & Hamer, 1967a) which involves use of a subsidiary extracorporeal indicator dilution circuit with a known flow rate feeding the same recording system as that used for the patient curve. Comparison of the curve area without recirculation by a known quantity of indicator (usually microlitre quantities) in the calibration circuit at known flow (usually ml/min) with the similar curve

area produced by indicator injection in the subject (usually in ml quantities) allows calculation of the cardiac output (usually in l/min). The similarity in size of the subject curve and the calibration curve minimizes errors due to non-linearity of the recording system. We have used this method successfully in human studies (Shinebourne *et al.*, 1967a) and recommend it as a simple and effective method for the calibration of coloured dye indicator dilution curves.

Left ventricular volume

The initial stimuli to the measurement of ventricular volume were the assessment of ventricular wall force from the Laplace relation ($F = \pi r^2 P$) and the investigation of the diastolic properties of the ventricular wall (pressure-volume relationship) as the basis of the initial stretch of the Frank-Starling mechanism.

Angiocardiographic techniques, pioneered by Arvidsson (1961) have quickly become established as a routine method for clinical assessment of left ventricular volume, and add little to the investigation as injection of contrast medium is generally required for diagnostic purposes such as the evaluation of mitral regurgitation. The contrast medium itself produces considerable haemodynamic disturbance due to the sudden increase in circulating blood volume, a vasodilator effect and the effects of coronary perfusion with hypertonic solution on myocardial performance, so the technique is not well-adapted to the study of interventions. A further problem is that ectopic beats frequently occur as the catheter tip touches the ventricular wall at the time of injection of contrast, and definitive measurements cannot be made until post-extrasystolic potentiation of contraction has subsided, by which time much of the contrast will have been lost from the ventricle reducing the definition of the ventricular cavity. Nevertheless with radiological techniques of high quality repeat measurements after an intervention have proved feasible (Coltart, Alderman, Robison & Harrison, 1975; Sharma, Goodwin, Raphael, Steiner, Rainbow & Taylor, 1976) Raphael, Zaidy & Oakley, 1976) using low doses of contrast. Timed injection in diastole may minimize the production of ventricular ectopic beats.

Analysis may be based on biplane or single plane cineangiogram frames or on separate films from a rapid film changer, and involve errors from the trabeculation of the inner wall of the ventricle which prevents clear delineation of the edge of the cavity, inclusion of the papillary muscle within the cavity outline and correction for magnification from the proximity of the X-ray tube and film as an angiocardiogram is recorded. It is usual to assume an ellipsoidal shape for the left ventricle (like a Rugby football) and to make volume calculations from a measurement of long axis and a single or both short

axes. In disease states any abnormality of movement of part of the left ventricular wall will produce a serious error in these calculations. It seems likely that this approach will be replaced in the future by radio-isotopic methods, using a gamma camera (Dymond, Jarritt, Britton & Spurrell, 1978) which detects the total indicator in the left ventricle and gives a volume measurement independent of left ventricular shape; this technique can be applied repeatedly with an intravenous injection as an almost non-invasive method, but requires expensive equipment for good results.

Indicator dilution methods

The conventional smooth indicator dilution curve is in fact an artefact of the slow response of the recording system as the concentration of indicator changes in a step-wise manner with each heart beat. A recording system with high frequency response will reveal these steps (Figure 1) and a consistent ratio between the steps during the decay slope represents the degree of emptying of the ventricle at each beat. From the same curve or from an independent measurement of stroke volume (cardiac output per beat) the end-diastolic and end-systolic volume of the ventricle can be calculated in the absence of mitral or aortic regurgitation. We have applied the cold saline indicator method to this technique using a fast-recording thermocouple, and have used it to study the effects of propranolol (Hamer & Fleming, 1967, 1969) and glucagon (Hamer, Gibson & Coltart, 1973) on left ventricular performance. The indicator does not affect ventricular function and the studies can be frequently and quickly repeated. Injection of cold saline into the left ventricular cavity gives the best steps, but the method relies on an even distribution of the indicator in the ventricle, so the apparent emptying ratio may be inconsistent for a few beats while this occurs. The technique is independent of left ventricular geometry, but is generally used with a different technique to measure cardiac output increasing the possibility of errors. We have shown good agreement with angiocardiographic methods for left ventricular diastolic volume (Fleming & Hamer, 1968).

Ejection fraction

Familiarity with the measurement of left ventricular volume led to the realization that the ejection fraction, i.e. stroke volume in relation to the end-diastolic volume provided a good overall index of the performance of the left ventricle as a pump (Noble, 1977). This ratio is constant at around 0.6 for normal animals of widely differing size, and seems to be restored by ventricular adaptation to large volume loads as in mitral or aortic regurgitation. It is

Figure 1 Examples of thermodilution curves from patients with aortic stenosis.

(a) From relatively mild aortic stenosis showing large clear-cut steps with each heart beat indicating a relatively large ejection fraction with rapid warming of the cold left ventricular injection. The scale is inverted so that cold saline produces an upwards deflection.

(b) From severe aortic stenosis with a low ejection fraction and small steps at each heart beat as the cold injection is slowly diluted in the ventricle, merging into a semblance of a smooth indicator dilution curve.

The step ratio (R) is related to the ejection fraction (F),

$$\text{as } R = \frac{ESV^*}{EDV} = \frac{EDV - SV}{EDV} = 1 - \frac{SV}{EDV} = 1 - F^\dagger$$

where ESV = end-systolic volume
 EDV = end-diastolic volume
 SV = stroke volume

by definition:

$$^*ESV = EDV - SV \\ ^\dagger F = SV/EDV$$

(reproduced with permission from Hamer & Fleming, 1967).

depressed by local as well as generalized myocardial problems and has been useful as a general index of left ventricular performance.

Although usually measured by angiocardigraphy the change in ventricular shape during systole (the diastolic ventricle is more nearly spherical) may give rise to errors unless the cavity is much dilated. The indicator dilution method for left ventricular volume (Figure 1) in fact measures the ejection fraction directly. However it may be that such a structurally

based measure of myocardial performance is not open to extensive change under the influence of drugs. When alteration in heart rate was prevented, Hamer & Fleming (1969) showed a significant increase in the ratio of the thermodilution curve steps from 0.701 to 0.728 after propranolol indicating a small reduction in ejection fraction in those severely affected patients with aortic stenosis. With the many variations from patient to patient in this technique it does not seem a promising test for drug studies as many measurements were needed to show a minor significant difference. It seems likely that radioisotope methods (Dymond *et al.*, 1968) will prove a more satisfactory approach to direct measurement of ejection fraction.

Stress testing

In many patients with cardiac disease the circulation in terms of filling pressure and cardiac output may be relatively normal at rest and abnormalities will be revealed by stress testing. Effects of drugs may be evident under these circumstances, and stress testing is essential to assess the effect of drugs aimed at treating phenomena produced by exertion, such as angina (Sharma *et al.*, 1976).

The most physiological form of stress is dynamic exercise but this is difficult to arrange in the horizontal position at cardiac catheterization, although there is the advantage that some of the initial adjustments such as the increase to maximal stroke volume that occur early in upright exercise have begun in the recumbent patient. The best approach to dynamic exercise at cardiac catheterization is the use of the stationary bicycle which can be locked to the catheterization table and also allows measurement of the work done. Because of the inconvenience of the bicycle, many have tried to mimic the effects of exercise by producing a tachycardia with a pacemaker catheter in the right atrium. This form of stress is clearly different to that produced by dynamic exercise as it lacks the component of peripheral vasodilatation and the sympathetic stimulus to the myocardium that accompanies the tachycardia of exercise. Nevertheless it has been useful as a stress test for the assessment of angina (Balcon, Maloy & Sowton, 1968) and the end-point may be suitably influenced by drugs.

An alternative approach to stressing the circulation is to use *isometric exercise*, usually sustained hand-grip (Donald, Lind, McNicol, Humphreys, Taylor & Staunton, 1967), which has the advantage of a static procedure with minimal disturbance of cardiac catheterization technique. The centrally mediated increase in heart rate, arterial pressure and cardiac output which teleologically seems designed to maintain flow in the compressed vascular bed of the skeletal muscle produces an increase in after-load while pre-load is unchanged (Awan, Vismara, Miller, DeMaria & Mason, 1977). The stress is brief and occurs under

observation, so it can be promptly reversed if adverse effects are seen. As it has been found useful as a test of left ventricular function (Amende, Krayenbuehl, Rutishauser & Wirz, 1972), isometric stress might be considered as a relatively simple technique for the study of drug effects in the diseased heart under increased load.

Drug studies at cardiac catheterization

The extension to and evaluation of preliminary animal studies in man is the basis of the pharmacodynamic aspects of 'clinical pharmacology' but the inherent risks of cardiac catheterization prevent its application to normal volunteer studies. Normal subjects are studied in this way only occasionally, for instance the assessment of a systolic murmur found to be physiological, and few investigators have the opportunity to accumulate data for drug studies on normal subjects. Useful information may be obtained from near-normals, such as mild aortic valve stenosis or the left heart in atrial septal defect although the normality of these situations might be questioned by some. Fortunately most drugs are designed for the treatment of disease and there is little ethical problem in asking consent for the study of a drug which is under consideration for treatment of the patient concerned. Our glucagon study (Hamer *et al.*, 1973) was carried out on this basis in patients going to cardiac surgery. Our propranolol study (Hamer & Fleming, 1967, 1969) was planned to use beta blockade to unmask a high risk group with more severe degrees of left ventricular failure requiring unusual compensatory sympathetic activity; unfortunately all our patients seemed similarly reliant on myocardial sympathetic drive.

With most drug studies it is usual to make control measurements first and then study the effect of the intervention, assuming that the patient remains in a steady-state throughout. This seems inherently unlikely in view of the great anxiety experienced by most patients undergoing cardiac catheterization, the gradual loss of effect of any premedication and the syncopal tendency often produced by manipulation of the blood vessels. In general a good unit can carry out cardiac catheterization without premedication, but if great anxiety is present a drug with little cardiovascular effect such as a benzodiazepine might be suitable. The general adaptation of the patient to the alarming circumstances of the cardiac catheterization room might be expected to improve haemodynamics, but in fact long-term studies (DeMots, Rahimtoola, Kremkan, Bennett & Mahler, 1976) have shown progressive diminution in cardiovascular measurements with the prolonged rest so any improvement demonstrated is likely to be real. It is important to carry out within-subject control measurements in all but the briefest studies.

Flow-guided catheterization systems

Some minimization of the disturbance required for cardiac catheterization arose from the discovery that fine soft plastic tubing fed into the venous circulation found its way with the blood flow into the pulmonary artery. The location of the catheter tip is determined by pressure measurement with a sensitive manometer. A few ectopic beats are often seen as the catheter tip passes into the tricuspid valve but the procedure seems to be a safe one in the relatively normal heart. The method seems to have originated in Scandinavia and I used it extensively at the National Heart Hospital; it has since been widely popularized by Grandjean of Lausanne as an office procedure. Application to the intensive care situation has been helped by the introduction of the Swan-Ganz catheter with a terminal balloon which can be inflated in a distal pulmonary artery to give measurements beyond the balloon of pulmonary venous pressure analogous to the pulmonary artery wedge pressure from a conventional catheter tip (Ganz, Forrester, Chanette, Donoso & Swan, 1970), and this has largely replaced the simple catheter method. The measurement of left ventricular filling pressure ('pre-load') has been helpful with indicator dilution output measurements (Bradley, 1977) in the study of drug actions in cardiogenic shock after myocardial infarction or following cardiac surgery. In the absence of special equipment it is reasonable to assume that if the pulmonary vascular resistance is normal the pulmonary venous pressure approximates to the pulmonary artery diastolic pressure. A raised pulmonary vascular resistance is unusual in acute cardiac problems, being more often associated with pulmonary venous congestion of long duration, as in mitral valve disease, or more rarely a chronic increase in left ventricular wall stiffness in aortic valve disease or cardiomyopathy.

Exercise studies

Resting studies, give little indication of the haemodynamic behaviour of the patient during normal daily activity. In the study of the effects of drugs in hypertension variations in the haemodynamic effects on exercise may assume great importance. The relatively normal control of peripheral vascular resistance on exercise with beta-adrenergic blocking drugs contrasts with the severe falls in blood pressure on exercise found with the formerly popular adrenergic neurone blockers which has been suggested as a possible provocative factor in cardiovascular complications such as cardiac infarction or stroke in the presence of arterial disease (Raftery & Goldberg, 1977).

The flow-guided catheter technique with a simultaneous arterial catheter has given useful information in the study of the effect of β -adrenoceptor-blockers (Figure 2). If slightly wider

Figure 2 Fick cardiac output measurements at a flow-guided catheter study of a patient with mild hypertension on bicycle exercise showing the effect of intravenous propranolol ○ (5 mg). ● Control measurements.

Oxygen uptake (centre) increases with work load but is little affected by propranolol.

Mixed venous oxygen saturation (left, PaO₂ sat) falls with work load and is lower at all loads after propranolol.

Cardiac output calculated from this data shows a progressive increase with work load but is lower at all loads after propranolol.

Propranolol reduces the cardiac output but oxygen consumption is maintained by a fall in mixed venous oxygen saturation.

bore tubing is used than is needed for pressure measurement alone, adequate blood samples can be obtained for conventional Fick cardiac output measurements and derived measurements give a useful haemodynamic profile of drug effect on exercise. Exercise for this study was carried out on a stationary bicycle which has the advantage of allowing direct measurement of the work being carried out at each stage. Although pulse rate changes with increasing work loads are achieved quickly it takes several minutes for the cardiac output adjustments to become stable, yet a further change occurs with adaptation to prolonged exercise. The best compromise seems to be to make the cardiac output measurement between the four and six minutes of exercise at each work load. A control and drug run at a number of work loads

makes a formidable study under these circumstances and only fit and co-operative patients are suitable.

Treadmill exercise is in some ways more physiological than the bicycle and avoids the added hand-grip (isometric exercise) effect seen with some subjects on the bicycle. Lack of familiarity with a bicycle in older subjects may favour the use of a treadmill, but one of the team must act as a 'fieldsman' when subjects new to the treadmill are being studied. On the treadmill no direct measurement of work is available and the exercise is recorded in more familiar terms as walking speed and gradient. For our hypertension studies (Shinebourne, Fleming & Hamer, 1967b, 1968) we devised a system using a conventional indicator dilution technique (blue dye) on the treadmill, with a venous catheter in one arm and an arterial catheter in the other and using dynamic calibration of the dye curves (Shinebourne, Fleming & Hamer, 1967a) to show the acute and chronic (Prichard, Shinebourne, Fleming & Hamer, 1970) effect of beta-adrenergic blocking drugs. Although the dye curve gives an instantaneous output and does not require the timed collection of expired air needed for the Fick measurement, the test should be carried out at a standard time between the four and six minute of each exercise load when a steady state is most likely to be achieved.

A possible disadvantage of these studies is that with most drugs the effect is so prolonged that the control study must be carried out before the drug study. Complex effects are taking place during this time as the patient becomes used to the procedure and anxieties subside. With an isolated heparinized system to draw blood for the dye curves the blood can be returned after each measurement and blood loss should be minimal and ought not affect the results of the second study. Any syncopal tendency due to arterial catheterization is generally overcome during exercise and it seems likely that valid comparison can be made of drug effect and control values during submaximal exercise. Blood levels of a drug given intravenously may be falling rapidly due to tissue distribution at this stage and subsidiary studies may be needed to ensure that a suitable drug effect is present at the time of 'steady state' measurement.

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