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 (preload) 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 \( F = \pi r^3 P \). 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