The Critical Assessment of the Experimental Techniques for Cardiac Performance

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Abstract

Clascical haemodynamks has been notably successful in defining the normal physiclogy of the Cardiovascular sysP m, but failed te provide a clear definition and early diagnosis of a functional im? airment of the myocardium, this failure is possibly attributable to madequacy of the moni osed variables of the conventional haemodynamics studies.
In this article, two common parameters of cardiodynamics, viz., cardiac output and first derivatives of the ventricular pressure (dP/dt), are discussed in order to find properties of cardiac muscle which could help in dstinguisbing alterations of ventricular performance (JPMA: 33:18, 1983).

Introduction

Classical haernodynarrrics, notably successful in defining the normal physiology of the cardiovascular system as well as the pathophysiology of congenital heart disease, has yet failed to provide a clear definition and early diagnosis of a functional impairment of the myocardium. fThis failure could be due to inadequacy of the monitored variables of the conventional haemodynamics studies. Apart from the parameters of haemodynamics such as blood pressure and mean blood flow, which are very indirect and insensitive indicators of myocardial function, parameters such as mean systolic ejection rate, stroke work and power and dP/dt are equally wanting.
These considerations combined with the development of new techniques aroused the interest of physiologists to appreciate that the heart is not only a pump but is also a muscle, the evaluation of whose properties could help in distinguishing alterations of ventricular performance. The following list of parameters of cardiac function shows some commonly used but not very sensitive expressions and also includes the recent and specific indices in which both pressure and volume have been used.
1. Cardiac output (C.O.) and stroke volume. 2.Mean systolic ejection rate. 3. Left ventricular work and contractility index. 4.Ventricular power. 5. Systolic time intervals. 6. Indices of cardiac response to exercise. 7. Ventricular volume and ejection fraction. 8. Left ventricular mass. 9. First derivatives ofthe ventricular pressure (dP/dt). 10. Haemodynamic correlates of myocardial 02 consumption. 11. External mechanical efficiency.
All these parameters are significant in the assessment of cardiac performance, but C.O. and first derivatives of the ventricular pressure will be discussed here in detail.
I.Cardiac Output (C.O.):- CO. is defined as the amount of blood ejected per unit of time (mVmin). Commonly used as an index of ventricular function, the C.O. is a relatively insensitive parameter for its assessment, being regulated by various factors, such as body O_2 requirement, venous return, mechanical loads and myocardial mass (Kelman, 1971). The C.O. of a normal man at rest is approximately 5 Lit/mm hut under different physiological conditions this value changes, e.g., during certain forms of anaesthesia C.O. may fall to 2. 5 L/min (Kelman, 1971), whereas it may increase to as high as 30 L/min during streneous exercise (Astrand ct al., 1964).
Several methods are available for the indirect measurement of C.O. but the FICK and indicator dilution methods arc the standard techniques for the measurement of C.O. because of their accuracy, safety, reproducibility and simplicity (Yang et al., 1972a). These two, alongwhh other methods will be

discussed in detail.

1. Direct Fick Method. (Fick, 1870):- Blood flow through an organ can be determined if a substance is re moved from or added to the blood during its flow through the org2n. The above Fick principle has been used in lungs to calculate the volume of the blood required tran: -port the C2 sken up from the alveoli per unit time. The direct Fick method employs the following formula C.C=O_2Consumprion m' /min X 100

A-V_2 difference

02 consumption is generally measured over a period of several minutes. A preferred technique is to collect all the expired air in spirometer over a timed period (usually 3 min and analysing samples for O_2 content in expired air. Comparison between O_2 contents in expired air and ambient air (volume should be the same in both cases) provides the data required to compute the O_2 uptake. O_2 consumption can also be measured with Nunn,s technique, the subject inspires an appropriate gas mixture from a rigid airtight box and then expires into a bag contained within the box. The change of volume of the total bag-box gives a measure of the difference between inspired and exoired minute volume (Kelman, 1971).

$$C.O. = \frac{1 \times 60}{A/B \times K \times t} = \frac{C \times 60}{Area \times t}$$

C.O. = Cardiac output
I = Amount of the indicator injected (mg)
60 = 60 sec/min.
A = Area under the complete curve (mm^2)
B = Base of the complete curve (mm)
K = Calibration factor mg/l/mm
t = Total curve duration (Sec)

Arteriovenous oxygen difference (A-VO_2) :-The arterial blood throughout the body normally has a - uniform O_2 content. However to determine a significant A-VO_2 difference it is necessary to know the content of O_2 in mixed venous blood. The mixed venous blood is preferably sampled from the pulmonary artery where the mixing is adequate, to gain the samples, a catheter is based through the venous channels into the right chambers of the heart.

$$C.O. = \frac{I \times 60}{cm \times t} = \frac{I \times 60}{Area} = \frac{I \times 60}{\frac{PC \times PCT}{3\text{-}0.9\,(PCT/AT)}}$$

$$= \frac{(C \times 60)\quad 3\text{-}0.9\,(PCT/AT)}{PC \times PCT}$$

$$\text{Flow } F = \frac{m \times 60\,(T_2 - T_1) \times SHR \times SGR}{A \times f}$$

where m = mass of injectate
T_1 = Temperature of saline
T_2 = Temperature of the body of the animal
SHR = Ratio of the specific heats of the blood and injectate
SGR = Ratio of the specific gravity of the blood and injectate
A = Area under the thermodilution curve
f = Constant

The cardiac catheterization is not free from dangers in that it can produce ventricular fibrillation (Bousvaros et al., 1962). The technique of cardiac catheterization and its source of error have been described in detail by Stow (1954). However, the catheterization of the right heart in order to obtain samples of mixed venous blood is a disadvantage (Kelman, 1971).

Arterial and venous O_2 content can be directly measured with vanslyke apparatus. This method though is very accurate, carried out by a highly trained person, but is time consuming. For rapid determination of blood O_2 contents, photo-electric method compares favourably with vanslvke method.

Apart from the cardiac catheterization as a disadvantage, there are few more con. iderations to test the validity of this method. Cardiac catheterization itself is too complicated a procedure to use in routine studies and is not entirely suitable for use during exercise. The other assumption in this technique that the rate o' C2 removal by the blood equals the rate of C2 upcake at the mouth dots not apply at the start of exercise. The compo. ;ition of arterial blood varies during respiratory or cardiac cycle. These variations may cause errors in the calculated C.0. in rest as well as in exercise.

2. Indicator Dilution Method :- In recent years the Fick technique has been challenged by the introduction of the indicator dilution method, being easier to 'use and not requiring either samples of mixed venous blood or the measurement of the body 02 consumption which may be experimentally dtfficult particularlv during anaesthesia.

Introduced by Stewart (1897) this method was based on the principle that volume of a fluid in a container can be calculated by adding a known quantity of dye and measuring the concentration of the material following even dispersal through the fluid. The volume can be calculated by the formula:-

V = A'C

where T = volume of the fluid

A = amount of dye added

And C =concentration of the dye in each cubic centimeter of fluid.

Stewart (1921), showed that his method can also be applied to. fluids in motion. Its usefulness was confirmed by Kin man et al. (1929) and Hamilton and Remington (1948), and its theoretical validity shown by Zierler

(1962). This method employs the Hamilton equation which is as follows:-

PC = Peak Concentration.

PCT = Peak Concentration Time.

The dotted line is the terminal portion of the indicator dilution curve expected to be without reci rculation.

A bolus injection of a certain amount of dye is given into the circulation via the jugular vein of the right side of the heart and blood is withdrawn through brachial artery at a constant rate. A time concentration curve can be recorded using a densitometer (Fig. 1).

$$C.O. = \frac{I \times 60}{Cm \times t}$$

CO = Cardiac output (l/min)

I = Amount of indicator injected (mg)
60 — 60 sec/min

Cm = Mean indicator concentration

t = Total curve duration.

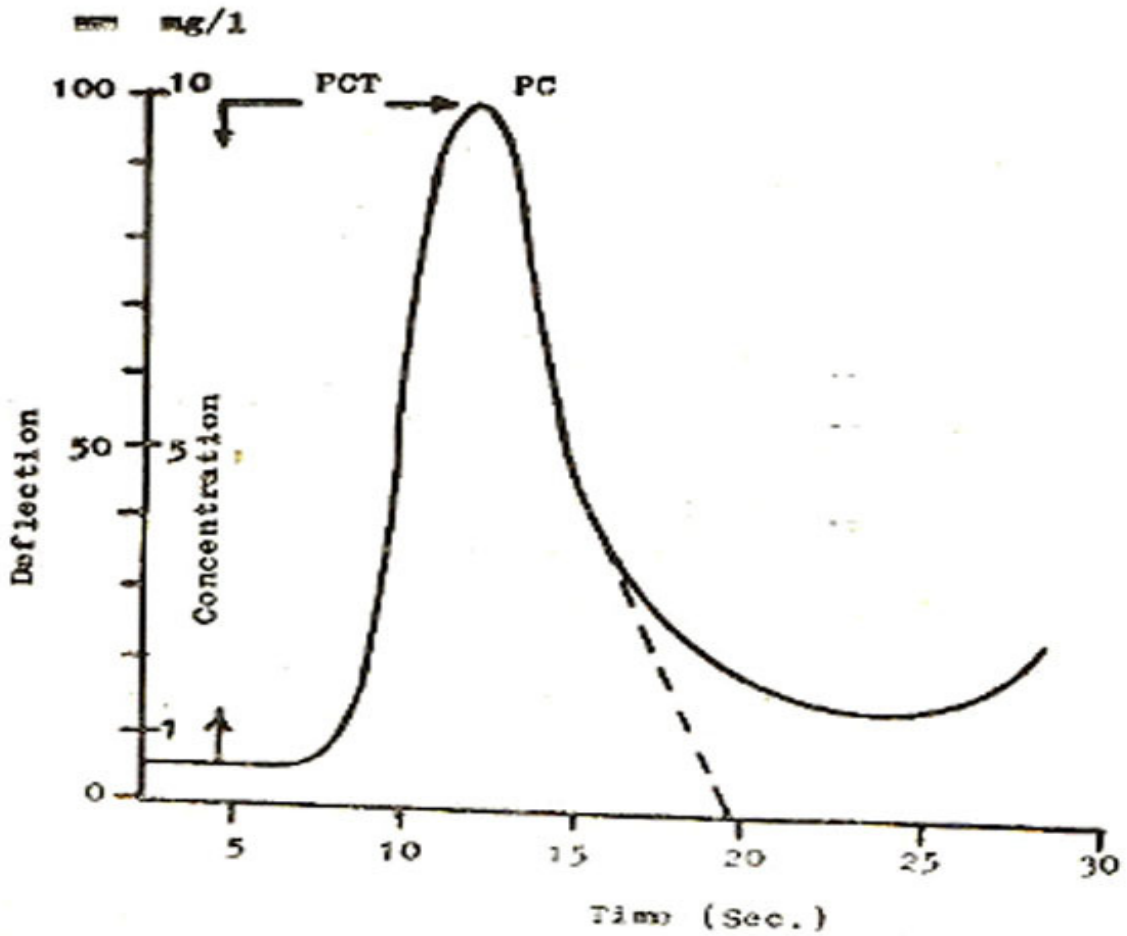

Fig. 1. Shows the Indicator (dye) Concentration (mg/L) measured as a Deflection on the Original Curve (in m.m.).

The rapid injection of indicator causes a sudden, transient high concentration of the dye in the venous blood. By the time the indicator has reached the arterial side of the circulation this concentration profile has become flattened and prolonged because different particles of blood take different pathways through the pulmonary circulation.

The time-concentration curve consists of initial rapidly ascending phase followed by a slower downstroke and a secondary recirculation curve, which occurs before the first pass effect has had time to fully decay. This recirculation curve poses a difficulty in the assessment of the mean indicator concentration. This difficulty can be overcome by extrapolating the descending limb towards the base. For practical purposes a point at which the indicator concentration is 1% of the peak concentration is (arbitrarily) chosen as the end of the disappearance time. The indicator dilution curve replotted on semilogarithmic paper is, therelore, extrapolated to this point (Fig. 2).

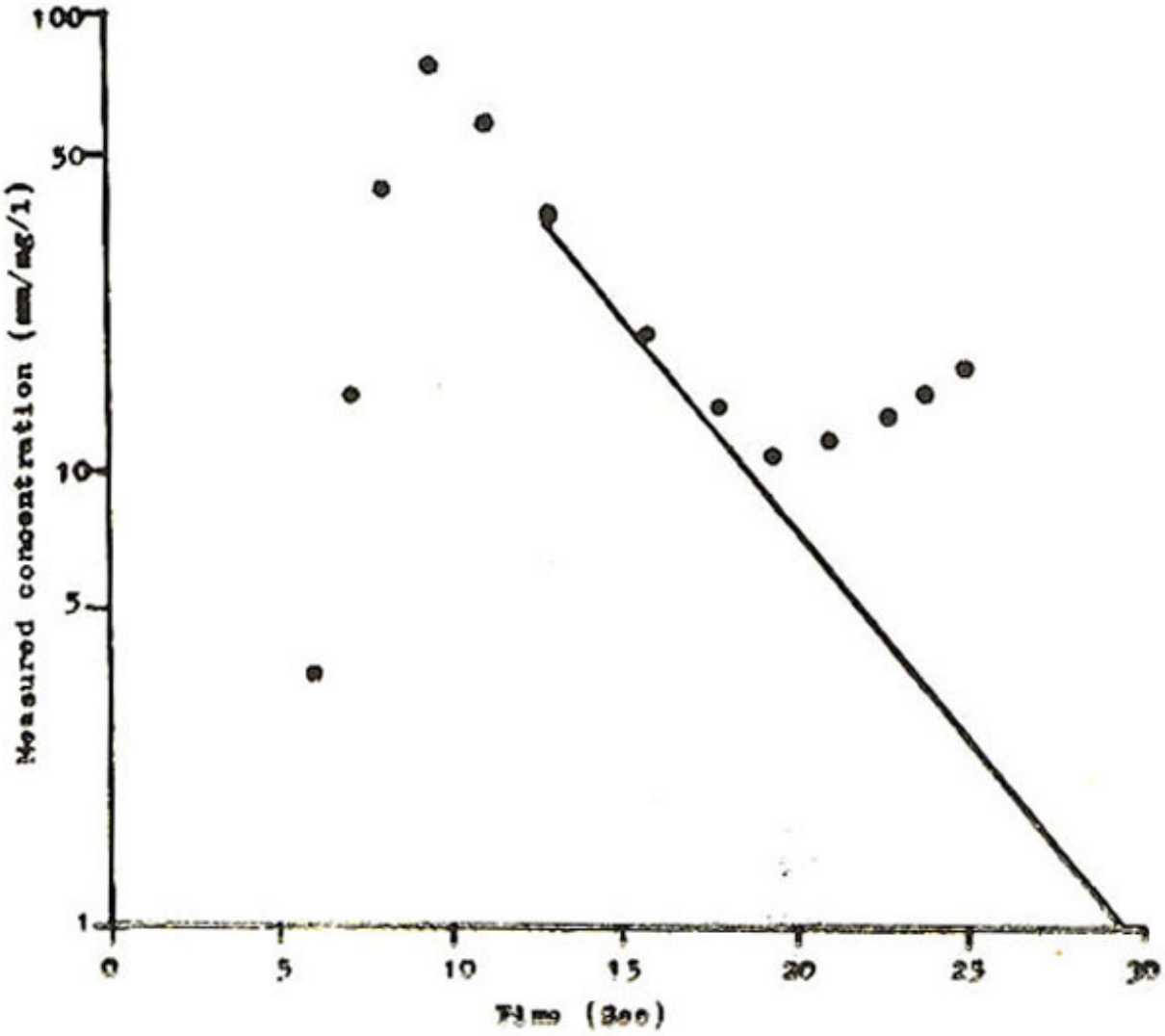

Fig. 2. Measured Concentration (mm/mg/L) of Indicator plotted against Time on Logarithmic axis. The solid line of Figure-2 is transferred to Figure-1 (dotted line).

Then the area under the curve (complete) plannimetered and expressed in mm2.
(Indicator concen trations (mg/1)
The calibration factor k =_____
deflection corres pondingly (mm)

was obtained by using calibration curve (Fig. 3)

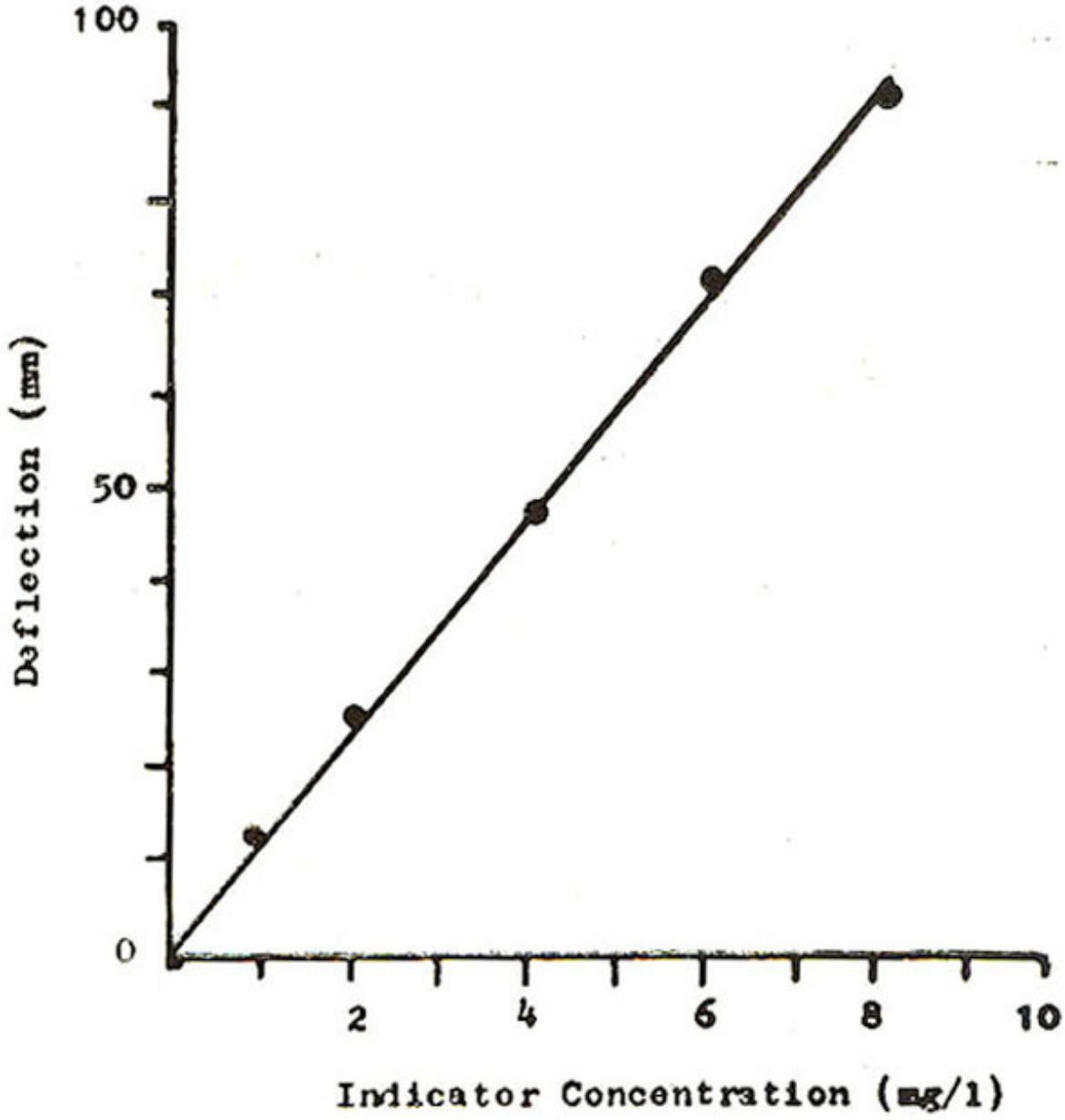

Fig. 3. Calibration Curve obtained by Sampling of known Dilutions of the Indicator through Densitometer and Recording the Deflection.

obtained by sampling the known quantity of dye through densitometer and measuring the deflection in mm. The base of the curve is also measured in mm. Now by the following formula CO. can be calculated.

The area under the normal indicator dilution curve may be determined in several ways. One meti.od is to utilize the sum of concentration time values (mm Sec) are read at one second intervals from the complete curve down to 1% of peak concentration. For this method the formula will be Where C1 = the

sums of the concentration time value (mm sec) read at one second intervals. The other method is Dow's method (Dow, 1955) which calculates the whole curve area from the peak concentration (PC) Peak concentration time (PCT) appearance time (AT) and two constant namely 3 and 0.9. According to this method the formula will be (Fig. 1):-

Coice of Indicator:- The best indicator for general use in experimental studies is the Indocyanine Green (cardiogreen), being non toxic even in larger doses and without adverse effects on the cardiovascular system (Kelman, 1971). It remains in circulation during its passage through the pulmonary capillaries. This dye is, however, expensive and unstable in aqueous solution.

Cold saline or Coolth is also a useful indicator. It is simple, inexpensive and nontoxic. The accuracy of the technique using Coolth depends on no loss of Coolth occurring between the injection and measuring points.

A simple method has been devised to measure the cardiac output by using thermistor probe and cold saline. The equation used for calculating the cardiac output is as follows (Moore et al., 1929):- f can be calculated at the end of the experiment by putting the thermistor probe (carotid probe only) into a beaker of saline at known temperature and deflection of the pend of the recorder was noted. From these values a graph can be plotted mm/oc from which the slope can be determined for use.

Radioactive microsphere are also in use for the measurement of CO. McDevitt and Nies (1976) showed in rat that simultaneous estimate-can be made by injecting" the carbonized microspheres labelled with 85Sr (15u diameter) in left ventricle over 20S and arterial blood was withdrawn from the femoral artery at 0.8 ml/min for 90 sec. This reference sample was used to calculate the CO by the formula

C.O=Counts injected x reference saw pie withdrawal rate reference sample rate

The radioactivity of the microspheres was determined by gamma scientillation counting before and after injection. The difference showed the amount of radioactivity injected.

3. Pulse contour method:- Erlanger and Flooker ^1904) recognised that the product of the pulse pressure and the heart rate indicated C.O., but with some reservations. There is a clear relationship between left ventricular stroke volume (SV) and the variation of aortic blood pressure during the cardiac cycle. When there is an increase in pulse pressure there should be an increase in SV. By recording the pulse pressure, it is theoretically possible to estimate continuously the SV and so of C.O. (Kelman, 1971).

This method gives beat-by-beat estimate of cardiac output but proved unsatisfactory for precise definition of the mathematical relationship between SV and pulse pressure (Rushmer, 1970).

4. Ballisto-Cardiography:- When the ven tricular contents are discharged into the arterial tree during systole, the remainder of the body experiences force in the opposite direction. The forces arising from the heart's action may be recorded by placing the oodv on a horizontally suspended platform equipped with means of measuring its movements. This record is known as ballistocardiograms (BCG). Many workers attempted to relate the magnitude of the BCG to SV. Most have conclud d that this relationship is qualitative rather than quantitative.

5. Catheter Flowmeters:- There are various kird ol flowmeters available hut their use is restricted to the animal research. These types are 1) Electro magnetic flowmeters, 2) Thin Film.

Electromagnetic flowmetcrs consist of a cuft placed around the exposed artery in art experimental animal. A modiLcation of this probe can easily be used in intact subjects, which has been developed in a way that such a flowmeter has been turned inside out so that blood flows over the surface of electromagnet and this flow causes an induced potential difference (PD) proportional to the flow velocity in the vicinity of the surface of the probe and this P1) can be detected with electrodes and, with the knowledge of the vessels cross sectional area, it is possible to calculate the total blood flow/mm.

Thin film catheter consists of a thin metal film, is deposited on the catheter and this catheter can be passed through the artery percutaneously. An electric current passed through the film raises the temperature, and blooci flow over this surface removes the heat by convection. The temperature of the film (its electrical resistance) thus gives a measure of blood flow.

In conclusion, the indicator dilution method seems to be better than others described above. In experimental studies flowmeters method may not be physiological as such that the opening of the chest of the animals is involved for the placement of the cuff round the aorta. Moreover it cannot be used in routine experimental studies due to lengthy surgical intervention. Ballistocardiography has not been reported in animal studies and it requires elaborate apparatus, even in clinical situation this method is more qualitative than quantitative (Kelman, 1971). Another drawback in this method is that the results may be seriously distorted by such factors as coupling between the body and the table, the elasticity of the skin acts as a spring interposed between the moving body, and the table top.

The Fick method although reliable is complicated and time consuming. One aspect in particular is hazardous in clinical situation, the cardiac catheterization. In experimental studies this method will not be able to give results continuously witn the changes in CO as the measurements will be irtermittent.

The pulse contour method can give beat-to-beat measurement of C.O but to define the precise mathematical relationship between stroke volume and pulse pressure have proved unsatisfactory.

When three methods have been compared, viz; pulse contour method, thermodi lution coil saline was used and flowmeter method, the results showed that determination by mathematical index (Pulse contour method) resulted in lower values for C.O., while thermodilution technique showed good correlation to values obtained by electromagnetic flowmetery. The thermodilution method has the advantage, however, of being less invasive than the electromagnetic flow method and provides absolute flow values unlike the index. The main disadvantage of thermodilution is that continual readings can not be made.

II. First Derivative of thc Ventricular Pressure.

The first time derivative of the ventricular pressure is “the rate of change of pressure with respect to time ‘ and usually expressed as dP/dt. Maximum value attained during early systole is designated as peak dP/dt (Yang etal., 1972 b). The maximal rate of left ventricular pressure rise (Max dP/dt and value derived from it have been used to evaluate the inotropic state of the heart in clinical Gleason and Braunwald, 1962; Mason, 1969) and in experimental situations (Reeves et al., 1960; Schaper et al., 1965).

The peak dP/dt has been used in the assessment of myocardial function, as it increases with increased contractility by digitalis action and the depressed myocardial contracti lity depresses the peak dP/dt. However, peak dP/dt also affected by the factors which are not related to the inotropic changes. Principal among these factors which alter peak dP/dt when contractility is stable are the loading conditions under which the heart operates. These loading conditions are: (Braunwalci et al., 1976a):-

Preload:- In the intact heart ventricular end-diastolic wall stress or tension is called- pre-load and determines the resting length of the muscle fibre. This preload on ventricular muscle can be altered (increased or decreased) by changing the end-diastolic pressure EDP and volume. It has been shown that increase in LVEDP also increased the peak dP/at (Wallace et al., 1963; Robie and Newman, 1975).

Afterload: It may be defined as the tension, force or stress in the ventricular wall during ventricular ejcction (Braunwald Ct al., l976b). Arterial diastolic pressure is a determinant of ventricular afterload (Mason, 1969). Elevation of arterial diastolic pressure influence the rate of rise of ventricular pressure during systole (Wallace et al., 1963; Wildenthal et al., 1969).

The other factor which effects dPfdt is heart ra.e. Any increase in heart rate causes an increase in the rate of rise of the ventricular pressure. Inherently related to an elevation of heart rate is an improvement in the fundamental contractile properties of the heart rate (Wallace et al., 1963). A direct linear correlation has been determined between peak dP/dt and heart rate in a variably paced canine atrial preparation (Wallace et al., 1963).

The development of indices to estimate contractility (dP/dt.

The various indices used to estimate contractility by indirect means in either ana- esthetized or conscious animals based on the appreciation of correction factors, which mainly concern the effect of loading condition (such as preload and afterload) of the heart. The following indices have been

developed to separate the effect of preload conditions on dP/dt from the effect of changes in contractility on dP/dt when afterload remains constant.

Time to peak dp/dt:- The time interval from the onset of ventricular contraction to the dP/dt max. denotes time to peak dP/dt (t-peak dP/dt) (Mason, 1969). It has been shown in intact canine preparations that, when t-peak dP/dt is shortened the peak dP/dt increases and an augmentation of mvocardial contractility is seen to occur (Mason et al., 1965). The combination of t-peak dP/dt allows a more precise estimation of directional changes in contractility than peak dPfdt used SC paratci V.

Isometric tension (Pressure) and end-diastolic pressure:- Another index of myocardial contractility has been based on the way in which alterations of end-diastolic fibre length of ventricular muscle affect the in- otropic stare (Mason, 1969). It has been demonstrated that a constant fraction of integrated systolic isometric tension (lIT) and the rate of development of isometric tension in isolated cat papillary muscle and the pressure in the isovolumic canine heart varies direci ly with changes in end-diastolic length of the fibre (Siegal and Sonnenblick, 1963).

When the measurements were made in the intact heart the ratio of peak dP/dt/IIT of the isolated papillary muscle is replaced by the ratio of peak dPfdt/IIP for the assessment of contractility free of changes in end-diastolic volume. The ratio of the dP/dtfITT or dPfdt/IIP is not affected by the magnitude of the preload (or fibre length) at a given stimulation rate but only mvocardial contractility (Seigal and Sonnenblick, 1963).

Peak dPdt/LVEDP (left ventricular end-diastolic pressure):- This index has been advocated for measuring the contractility by Reeves et al. (1960). They showed a significant correlation between maximum rate of pressure rise with ventricular end-diastolic pressure (r .468). This index is influenced by changes of arterial diastolic pressure (afterload).

Peak dP/dt/LVEDV (Left ventricular end-diastolic volume):- This index has shown in dogs a fairly good correlation with mvocardia I contractility. But much overlapping has been reported with control state and with increased afterload (Braunwaki et al., 1969). In hypertrophy condition in which increased muscular mass tends to raise peak dP/dt this index could falsely suggest just the opposite (Yang et al., 1972b).

dP/dt/MIT:- Frank and Levinson (1964) suggested that the ratio of peak dP/dt to maximal isovolumic tension (MIT) is useful as an index of contractility. MIT can be calculated from the determination of end-diastolic volume and peak isovolumic pressure. This MIT can be substituted with MIP and can be defined as the highest isovolumic left ventricular pressure in mmHg. This index has been proposed as a result of the observations that the index dP/dt/IP showed a significant correlation with fibre length (Yang et al., l972b).

Correction Factor for afterloads:- The parameter derived from the peak dPfdt which corrects for afterload is denoted as clP/dt/CPIP. CPIP is the maximal developed isovolumic pressure in mmHg which is common to both control and the altered state dP/dt is the rate of development of pressure in mmHg/ sec at the instant CPIP obtains for each state.

The above concept (that the relation between dP/dt and developed pressure throughout the course of isovolumic contraction) has been formulated, in an attempt to provide an accurate measure of ventricular contractility independent of afterload (changes of arterial pressure). For these studies and intact canine left ventricular preparation was prepared with a right heart by pass in which ventricular end-diastolic and aortic pressures, heart rate and the contractile state could be controlled indcpendently (Mason et al., 1967). When the aortic diastolic pressure (afterload) was altered even a very wide range and other parameters were kept constant, it was observed that the relationship of dP/dt to developed isovolumic pressure was not influenced by the pressure at which the aortc valve opened.

In conclu ion peak dPfdt (maximum rate of rise of the ventricular pressure) is tepcnd nt on the lo ading cond tions (preload and afterload) of the heart, heart rate and contractile state of the ventricle. When the loading conditions are stable peak dP/dt provides a sensitive means for the evaluation of changes in contract 11-itv. The elevation of ventricular end-diastolic (preload) or aortic diastolic pressure

(afterload) result in elevations of peak dP/dt. It has been shown in holated papillary muscle and intact canine ventricles that, when preload is stable and afterload varies the effect of variation or aortic diastolic pressure on dP/dt can be neutralized by comparing dP/dt at common isovolumic pressures. In this way a simple and useful method for the assessment of myocardial contractility during alterations of afterload has been provided.

The methods for measuring the cardiac performance which have been discussed are not free from criticism, especially the incorporation of the findings in isolated cardiac muscle preparation (Papillary muscle to the intact heart). Brutsaort and Paulus (1977) pointed out that pragmatic usefulness being only the justification for applying isolated muscle concept to the intact ventricle is no longer a sufficient argument.

The ventricle function is as a combined muscle-p7mp system and not as a papillary muscle and even less a simple tension muscle. The nature of loading forces which occur during muscle shortening in the ventricular wall in intaft heart arc quite different from those encountered in isolated muscle since the ventricle is not called on to sustain a weight but to eject a viscous fluid into a viscoelastic vascular system (Abbott and Gordon, 1975).

Moreover difficulties have been reported of attempts to use the method of extrapolating the plot of LV dP/dtJP against P to Zero P to obtain Vmax (Van Den Bos et al., 1973). Suggestions have been put forward to make progress in the field of measurement of ventricular function by conducting experiments that should be designed to distinguish between the relative contributions of muscular mechanisms and those of the ventricular configurational mechanisms underlying starlings law of the heart (Brutsaort and Paulus, 1977). However so far the index of Vmax has been favoured both in animals (Nejad et al., 1971) and in the clinic (Mason et al., 1970) as a suitable and accurate method determining the rate of rise of pressure in ventricles.

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