When measuring blood flow by the dilution method it is possible to inject an indicator either "instantaneously," i.e., in a minimum time, or it may be injected at a constant rate during a given period of time. The "instantaneous" injection is generally used whereas the constant rate of injection, owing to technical difficulties is used rarely, although Stewart used it. Fegler, in his studies on thermodilution, drew attention to the advantages of negative heat when used as an indicator. Since then, many authors have repeated Fegler's experiments and modified his method. The possibility of using the constant rate of indicator injection for measurements of cardiac output by the thermodilution method has not yet been evaluated in previous reports. If certain theoretical assumptions are valid, the method of constant rate injection of the cool indicator might extend the advantages of the thermodilution technique. For this reason it was decided to prove this possibility with the following experiments.

Methods

The accuracy of measurement of cardiac output by the constant rate injection of thermal indicator and the detection of heat dilution is dependent upon the degree to which the following conditions are fulfilled: 1. Complete mixing of the cool indicator with blood flow. 2. Heat exchange between indicator and blood takes place within the vascular bed only, where the blood flow is being measured. Heat exchange with adjacent tissues is negligible. 3. During the course of measurement the blood flow and its temperature are constant (except for fluctuation resulting from cardiac ejections). 4. During the measurement there is no recirculation of the cool indicator. 5. The shortest distance is taken between the place of the indicator injection and the place of thermodilution detection to reduce the influence of any transitory phenomena and to obtain a thermodilution curve plateau that would be well-defined and of satisfactory duration. 6. The indicator injection causes a reduction of the measured flow. The value of this change is dependent upon the amount of indicator and the method of injection into the blood flow.

If the conditions mentioned above are fulfilled, the following equation is obtained for the measured blood flow:

\[ F = 60 \cdot f_i \cdot \frac{T_v - T_i}{T_b - T_v} \cdot \frac{c_i \cdot s_i}{c_b \cdot s_b} + 60 \cdot K_m \cdot f_i \]  

(1)

where:

- \( F \) = blood flow, ml/min
- \( T_b \) = blood temperature, °C
- \( T_i \) = indicator temperature at point of injection into the circulation system, °C
- \( T_v \) = temperature after mixing blood with the indicator, °C
- \( f_i \) = indicator flow, ml/sec
- \( c_i \), \( c_b \) = indicator and blood specific heat, cal/g/°C
- \( s_i \), \( s_b \) = indicator and blood specific weight, g/cm³
- \( K_m \) = constant, depending on mode of indicator injection.

Since

\[ K_m = \frac{1}{f_i} \cdot \frac{\Delta P}{R} \]  

(2)

where:

- \( \Delta P \) = pressure increase at the point of indicator injection into the circulation system, dyn cm⁻²
- \( f_i \) = as in equation 1, cm³ sec⁻¹
- \( R \) = flow resistance in the circulation system between the point of maximum pressure
and the point of indicator injection, dyn/cm²/sec, it is possible to attain 

\[ K_m = 0, \text{ with a low kinetic energy indicator, on which } \Delta F \text{ is dependent, and an indicator point, on which } R \text{ is dependent.} \]

Then the following equation may be used for the measured flow:

\[ F = 60 \cdot f \cdot \frac{T_o - T_i}{T_b - T_o} \cdot \frac{c_i \cdot s_i}{c_b \cdot s_b} \]  

(3)

The indicator at room temperature is heated during its passage through the intravascular part of the catheter. This change requires a correction which has to be measured in a model experiment. If the indicator temperature is known before it is injected into the catheter, then its temperature at the point of injection into the blood is

\[ T_i = T_i' + \frac{2}{k \cdot l_o} \left( \frac{2}{k \cdot l_o} \cdot \frac{T_o - T_i}{T_b - T_o} - 1 \right) = 0.25 \]  

(4)

where

- \( T_i' \) = indicator temperature before injection into catheter, °C
- \( T_o, T_b, c_i, s_i, f_i \) = as in equation 1
- \( k \) = coefficient of heat transfer through catheter wall when blood and indicator flow have the same direction, cal/cm⋅sec⋅°C
- \( l_o \) = length of catheter in the vessel, cm

The experimental verification of the above-described assumptions was first investigated in model experiments. With a stabilized pump distilled water was drawn from a thermostatically controlled bath through thermally insulated tubing. The inner diameters of the tubes were 5, 8, 13, and 20 mm. A calibrated rotometer was inserted into the circuit but during the experiment flow was also measured volumetrically. The temperature of the flowing fluid was stabilized within ±0.02°C by an electronic apparatus which was adjusted from 38.5 to 39.0°C in various tests. The indicator (distilled water) of stabilized temperature (18.00 to 22.00°C) was injected with a mechanical device through the catheter at a constant rate of flow (0.8 to 2.2 ml/sec). The injection took 8 to 10 seconds. The indicator was injected upstream from the measured flow from a jet with a diameter of 0.3 to 0.5 mm. A second catheter with a thermistor mounted within the catheter tip was located down the flow stream at a distance of 0.5 to 30 cm. The distance between the injecting jet and the thermistor is called the detection distance. A thermistor* with heat co-efficient 3.5%, was used for the thermodilution detection. After the thermistor had been mounted into the catheter, the time constant was less than 1 second. The thermistor was incorporated into the arm of the Wheatstone bridge. The output was fed into the d-c preamplifier and recorded with a direct-writing apparatus. The bridge voltages were attenuated so that heating of the thermistor was not sufficient to make them sensitive to changes in flow. Model experiments were used to examine the influence of the injection of indicator on the measured flow. The indicator was injected upstream, downstream, and perpendicularly to the direction of the liquid flow.

For measurement of cardiac output in dogs it was necessary to determine the correction of indicator temperature in the model. Various catheters, used for indicator injection in dogs, were introduced under fluoroscopic guidance and their position verified at autopsy. An 0.9% NaCl solution or a 5% glucose solution at room temperature was used as an indicator. This was injected mechanically at a constant rate of 1 to 2 ml/sec. The volume of the injected indicator was chosen so as to produce a sufficient difference at the point of detection between the original blood temperature and the temperature of blood mixed with indicator \( (T_b - T_m = 0.25 \text{ to } 0.40°C) \). The time of indicator injection depended on the attainment of the apparent curve plateau.

In order to check the influence of the injected indicator upon the measured blood flow, the pressure in the right atrium and the right ventricle was measured during injections of indicator into these sites.

From the total number of animals nine dogs were used to compare the proposed method with two control methods. During the first part of the experiment the cool indicator was injected alternately "instantaneously" and continuously at a

*Catheter with a thermistor mounted within the jet with a diameter of 0.3 to 0.5 mm. A second detection distance. A thermistor* with heat co-efficient 3.5%, was used for the thermodilution detection. After the thermistor had been mounted into the catheter, the time constant was less than 1 second. The thermistor was incorporated into the arm of the Wheatstone bridge. The output was fed into the d-c preamplifier and recorded with a direct-writing apparatus. The bridge voltages were attenuated so that heating of the thermistor was not sufficient to make them sensitive to changes in flow. Model experiments were used to examine the influence of the injection of indicator on the measured flow. The indicator was injected upstream, downstream, and perpendicularly to the direction of the liquid flow.

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*Type 13 NR 17 VUPEF, Prague.
constant rate. The areas under the curves were measured with a planimeter after injection of 5 ml indicator. A total of 42 pairs of curves recorded at intervals of five minutes were compared. In addition, 32 pairs of simultaneous cardiac output measurements by the Fick principle and by the proposed thermodilution method were used for the second comparison. Oxygen consumption was measured with a respirator. Oxygen content in the blood was measured by an oximeter.* Samples of blood were always taken before and after injection of the cool indicator. Only those measurements of cardiac output were taken for comparison in which the respiration and circulation were in a steady state and where the arterial blood was fully saturated (above 95%).

Results

Model experiments indicated that under experimental conditions, in most cases, satisfactory mixing takes place at a distance greater than 20 cm. In tubes with larger diameters before and after injection of the cool indicator. Only those measurements of cardiac output were taken for comparison in which the respiration and circulation were in a steady state and where the arterial blood was fully saturated (above 95%).

* Elema.

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and greater flow rates, such complete mixing cannot be accomplished as in tubes with smaller diameters. In the latter, indicator quantity was too small in relation to the quantity of the measured flow. The shorter the distance of detection, the more random the degree of thermodilution detected by the thermistor (fig. 1). In shorter sections it is possible to achieve only partial improvement of mixing by increasing the indicator injecting rate, or by increasing the number of jets. At a detection distance of 25 cm, the flow values computed, according to the thermodilution curves, appeared to be somewhat higher than the actual flow. With a 5-mm diameter tube the flow computed was higher by \( +1.9 \pm 2.1 \% \); with 8-mm diameter, \( +2.2 \pm 1.3 \% \); with 13-mm diameter, \( +8.9 \pm 2.1 \% \); and with 20-mm diameter, \( +9.4 \pm 5.8 \% \) (arithmetical mean ± standard deviation in per cent).

It was shown in model experiments that constant rate indicator injection, directed against flow direction of the measured liquid, reduces the measured flow by approximately \( \Delta F \approx 0.3 \cdot f_i \). When injected perpendicularly to the stream direction it is reduced approximately by \( \Delta F \approx 0.2 \cdot f_i \). The smallest reduction is recorded when the indicator is being injected downstream, \( \Delta F \approx 0.1 \cdot f_i \). It is obvious from these measurements that there is only a small change occurring in the measured flow, dependent on whether the indicator is injected downstream or into the stream (about 1% of the measured flow).

In experiments on dogs we investigated mixing the indicator with blood in the region between the orifice of the vena cava and the pulmonary artery trunk. In the first series of experiments we recorded the blood temperature in this region. The temperature of the blood in the superior vena cava was lower (0.5 to 1.0°C) than that in the inferior vena cava. Blood temperature in the right atrium fluctuates near the average temperature value in the vena cava. The amplitude of temperature changes near the tricuspid valve is 0.04 to 0.08°C. In the direction of the outflow tract of the right ventricle, the fluctuation in temperature decreases. In the region of pulmonary artery valves, temperature fluctuation reaches maximally 0.04°C and does not change when the thermistor catheter is advanced 3 to 5 cm into the pulmonary artery trunk. Temperature fluctuations in the pulmonary artery were dependent on respiratory cycles only. In some cases we did not observe any measurable temperature variations in the pulmonary artery, even after changes in the position of the catheter.

During the second series of experiments the indicator was injected repeatedly, in quick succession, into different parts of the vena cava, right atrium, and right ventricle. The dilution curves were alternately detected in the outflow tract of the right ventricle and in the pulmonary artery. In steady state of circulation the best reproducibility of curves was attained when the indicator was injected into the right atrium close to the tricuspid valve, and the thermodilution detected in the pulmonary artery (fig. 2). The position of the thermistor in the region between the pulmonary valve and proximal part of the pulmonary artery branches had no effect upon the reproducibility of the flow rate measurements.

![Graph](image-url)
We also measured, in quick succession, the cardiac output by injecting the indicator through two to four radially arranged apertures on the catheter tip and by injections through the whole catheter diameter. The reproducibility of measurements was lower when the injection was made through radially arranged jets than when given through the whole catheter diameter. When the injection was given through jets into the right atrium, sinus bradycardia frequently occurred, while injection into the ventricle caused premature beats. A sensitive continuous recording of pressure in the right atrium and ventricle showed that no measurable changes of pressure occurred in the course of indicator injection. According to equation 2 the value $K_m$ is thus negligibly small and equation 3 is suitable for the computation of flow.

The degree of heat exchange between blood...
and indicator mixture on one hand, and walls of the circulatory system on the other, have not been measured directly. It is possible to estimate it indirectly from the form of curves. During the course of indicator injection, a cooling of cardiac walls occurs. The curve plateau indicates that heat exchange has reached a certain balance. Usually the descending part of the curve, after the accomplishment of indicator injection, does not attain the level of the original temperature rapidly but is considerably prolonged. This indicates that a reversible heat exchange is occurring between the blood flow and cardiac walls.

From the base line of the curve the stability of blood temperature may be judged and, from the curve plateau, the stability of blood flow. If greater irregularities occurred in the curves, they all corresponded to very quick changes in heart rate and blood pressure and to single deep inspirations (fig. 3).

Since the recirculation of cool indicator and blood mixture were not clearly manifested in the form of thermodilution curves, it was checked by measurements of blood temperature in the pulmonary artery trunk after indicator injection into left ventricle or left atrium. In other experiments blood temperature was measured in the outlet of the inferior vena cava and the indicator was injected into the pulmonary artery trunk. After passage through the systemic circulation, the recirculation wave in the pulmonary artery reached a maximum of 1% of the systemic curve height. In these experiments the total circulation time was always longer than eight seconds. In some experiments, especially in unanesthetized dogs, no measurable recirculation occurred. In some cases recirculation manifested itself as an inconspicuous rise of the curve plateau about ten seconds from the beginning of the curve. This inconspicuous rise can be masked by respiratory fluctuation of the curve plateau. If the indicator is injected in a sufficient quantity in relation to the value of the measured cardiac output, then temperature fluctuations of the curve plateau indicate fluctuations of the right heart output only (fig. 3).

Thermodilution measurements of cardiac output by the method of “instantaneous” injection showed an average value of 2.65 ± 0.245 liters/min. Five minutes later, measurements made by the method of constant rate injection of indicator had an average value of 2.55 ± 0.250 liters/min. The 4% difference in means is not statistically significant. Simultaneous measurements of cardiac output by the proposed method and by means of the Fick principle under steady state circulation showed good agreement between the two methods (correlation coefficient \( r = 0.98 \)). Even though there is no systematic difference in measurements, the maximal differences are +15.5 and −16.0% (fig. 4).

**Discussion**

Model experiments showed that complete mixing of indicator with measured fluid takes place along a definite route and at a definite time. With tubes of large diameters the flow values, computed according to the thermodilution curves, appeared to be somewhat higher than the actual flow. The direction and extension of this deviation is obviously
caused by the indicator mixing with the flowing liquid (at temperature $T_v$), and being warmed by the tubing wall (temperature near $T_b$). With tubes of large diameter the flow rate is much lower and consequently there occurs a much greater heat exchange between the flowing mixture and the tubing wall. Thus we substitute somewhat higher $T_v$ in the formula which causes the observed error in model experiments.

Differences in blood temperature in the vena cava, superior and inferior, recently described in detail, decrease in the right ventricular outflow tract. This is interpreted as gradual mixing taking place in the region between the right atrium and the trunk of the pulmonary artery. The degree of mixing in the pulmonary artery has been considered satisfactory for dilution measurements.

It has been repeatedly shown that heat transfer, between the walls of the central circulatory system and the cool mixture of indicator with blood, was almost completely reversible and did not cause error in measurement when the indicator had been injected "instantaneously." Only when the indicator is injected more peripherally and/or thermodilution is detected in a peripheral artery, are the resulting values of cardiac output significantly higher. When the indicator injection is at a constant rate, it is different, even when the detection distance is short. During injection the cardiac wall becomes cool, while the cooler mixture of blood with the indicator becomes warmer. The curve plateau shows the achievement of a balance in the heat exchange. Results of measurements of flow, based on curve plateaus, do not manifest a systematic tendency toward values that are higher than measurements according to the Fick principle or thermodilution by "instantaneous" indicator injection. We deduce from this that, at the time when the thermodilution curve reaches the plateau, the heat exchange between the walls of right heart cavities and their content is minimal.

The form of each curve is the only factor from which we can estimate the degree to which theoretical assumptions of temperature and blood flow constancy during the measurement are met. The possible recirculation of cooled blood is negligible for two reasons: 1) Heat exchange in systemic capillaries is rapid. 2) The total circulation time of 9 to 13 seconds is long enough to allow the curve to reach a satisfactory plateau.

Thermodilution measurements have been computed according to a formula from which we can deduce that, during the indicator injection, the measured blood flow is reduced by its volume. However, the validation of this was lacking. When the indicator injection point was chosen at the place of minimal pressure in the vascular bed (right atrium) and an indicator of low kinetic energy was used (injection through the broad catheter opening), it was possible to neglect the influence of the indicator on the measured flow and compute the cardiac output according to equation 3. This is confirmed by the results of flow measurements in model experiments and of pressure recording in the right heart at simultaneous indicator injection.

The precision of measurements by the proposed method was evaluated according to the reproducibility of measurements and the absolute values were compared with simultaneous measurements using the Fick principle and with alternating measurements by thermodilution with "instantaneous" indicator injection. The results are in agreement with those reported for the thermodilution method. The occurrence of single examples of conspicuous differences cannot be explained and the absolute accuracy cannot be evaluated since standard methods used currently also show considerable differences.

Measurements of cardiac output with use of the cool indicator have several advantages in comparison to those made with the dye indicator. The mixing of the cool indicator is more efficient. The intravascular detection of thermodilution eliminates the distortion caused by the dye sampling system as well as the loss of blood which takes place in the course of sampling. Due to the negligible recirculation of indicator, there is no need to
extrapolate the descending part of the curve.13, 14, 19 The calibration of heat change is much simpler than that of dye concentration. The proposed method for measurement of cardiac output retains the above-mentioned advantages of thermodilution and reduces the influence of transitory changes which occur during "instantaneous" injection of the indicator. The temperature of the indicator changes in the intravascular region of the catheter because the first portion of the indicator is warmer than the last portion.18 Mixing of indicator with blood in the right ventricle and the heat exchange with the walls of cardiac cavities is more random due to its transitory character. This is eliminated considerably by constant rate indicator injection. A practical advantage of the proposed method is a considerably quicker computation of the cardiac output value since planimetry of the area under the curve is eliminated. With use of an appropriate nomogram it is possible to calculate the cardiac output value during the course of the experiment. The disadvantage of this method is the greater quantity of indicator required and the greater time interval between determinations.

Summary

A mathematical formula has been suggested for measurement of cardiac output by the thermodilution technique using constant rate indicator injection. The theoretical assumptions have been checked in model experiments and in experiments on dogs. The best reproducibility was attained when the indicator was injected into the right atrium, near the tricuspid valve, and the dilution was detected in the pulmonary artery. Recirculation of the cool indicator is negligible and takes place only after the attainment of the curve plateau. No systematic difference was found in simultaneous measurements made by the Fick principle and the injection technique. The correlation coefficient, r, was 0.96.

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CARDIAC OUTPUT BY CONSTANT INJECTION


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