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Bepaling van de gemiddelde bloedstroomsterkte met indicatorenverdunningsmethodes.

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1969

Citation for published version (APA):
Hoor, F. T. (1969). *Bepaling van de gemiddelde bloedstroomsterkte met indicatorenverdunningsmethodes.* s.n.

Summary

Chapter 1

Although Grollman[98] was convinced that the determination of cardiac output in man could be accurately carried out with the acetylene-method, results obtained with the direct Fick and other indicator dilution methods do not support this conclusion[288]. Therefore a critical evaluation of the methods in use for the determination of cardiac output is desirable; in this book some of the methods have been analyzed. In section 1.2 $\dot{Q}_s$, $\dot{Q}_p$, $\dot{Q}_x$, $\dot{Q}_y$, $\dot{Q}_b$ and $\dot{Q}_f$ are defined (fig. 1); the recurring symbols and abbreviations are summarized in table 1. In 1.3 a survey of literature data concerning the normal cardiac output in man and some animals (tables 2 and 3) is given. The value of the concept of cardiac index is discussed using data from Jegier *et al.*[136], Brotmacher and Deuchar[26], Smulyan *et al.*[240] and Guyton[104]. As the correlation between cardiac output and body weight is as good as the correlation between cardiac output and body surface area, while the calculation of body surface area from height and weight is rather inaccurate[153,231], it is concluded that cardiac output should be expressed in $1 \cdot min^{-1} \cdot kg^{-1}$.

Chapter 2

In section 2.1 a survey of early estimates of left ventricular stroke volume in man has been given first (table 4). The methods now in use for the determination of cardiac output may be divided into direct, indirect and empirical methods. *Direct* are those in which some physical quantity directly related to the blood flow is measured. A survey of these methods has been given by Van der Werf[273]. In the *indirect* the mean blood flowrate is calculated from measurements of the transport of an indicator by the blood. Except for the bubble flowmeter, all indirect methods are indicator dilution methods. *Empirical methods* are based on an empirically established relationship between some quantity observed and the blood flowrate; these methods are excluded from the discussions.

In 2.2 the Fick-principle is described (fig. 2; equations (2) and (3)) and a survey given of the development of the direct and indirect Fick methods. Special attention has been paid to the continuous cardiac output computer developed by Guyton *et al.*[105,106,107] (fig. 3). In almost all indirect Fick methods the indicator used is CO_2. The earlier breath-holding and rebreathing

methods for the determination of $P^{\bar{v}}_{CO_2}$ are mentioned; the methods of DuBois *et al.*[61], Defares *et al.*[49,51,52] and Kim *et al.*[140] are discussed. In section 2.3 the principle and the development of the method of Stewart-Hamilton (figs. 8 and 9; tables 7-11) are described; in section 2.4 an account is given of the "foreign" gas methods, especially the acetylene method and the method for the determination of stroke volume using a body plethysmograph and N_2O.

Chapter 3

In section 3.1 a theoretical analysis of the Fick-principle according to Cropp and Burton[47,48] has been presented. It is concluded that their "wrong mean error" and their "distance distortion error" do not significantly disturb the Fick method; changes in respiration are probably more important. A theoretical comparison between the direct O_2-Fick and the direct CO_2-Fick shows that the direct CO_2-Fick is considerably less accurate than the direct O_2-Fick.

In 3.2 some methods for the determination of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are described. Special attention is paid to the diaferometer (3.2.3). This apparatus was calibrated with expired gas using the set-up of fig. 14. The derivation of the equations for the calibration with expired gas and for the determination of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ is given in the equations (42) - (79) (see also fig. 13). Methods for the determination of $c^b_{O_2}$ and $c^b_{CO_2}$ are described in 3.3. Among these, the method of Van Slyke is the most accurate. In table 15 the results of a statistical analysis of duplicate determinations of $c^a_{O_2}$ and $c^{\bar{v}}_{O_2}$ using the manometric method of Van Slyke are summarized.

Data from the literature as regards the comparison of the direct O_2-Fick with the direct CO_2-Fick are given in fig. 15 and table 16. In 3.4.2 the results of 40 simultaneous determinations of the direct O_2-Fick and the direct CO_2-Fick in dogs are communicated. In the experiments $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were determined with a diaferometer (fig. 16) which was calibrated with expired gas of dogs (fig. 17 and table 18); $c^a_{O_2}$, $c^a_{CO_2}$, $c^{\bar{v}}_{O_2}$ and $c^{\bar{v}}_{CO_2}$ were determined with the manometric method of Van Slyke. Using the dilution method, cardiac output determinations quasi-simultaneous with the direct Fick were performed (see chapter 6). The results of the comparison between the direct O_2-Fick and the direct CO_2-Fick are given in table 19. Table 20 shows the errors possible when using the direct Fick method for the determination of cardiac output.

Chapter 4

In section 4.1 some practical and theoretical aspects of the indicator dilution methods have been discussed. Fig. 19 shows the possible influence of respiration, fig. 20 the slight influence of the indicator injection on the determination of cardiac output with the dye dilution method. In the experiment of fig. 21 there was no demonstrable influence of extrasystoles on cardiac output. The relation between instantaneous and continuous injection of indicator is shown in the equations (85) - (89), fig. 22 and the tables 21 and 22. A method for the extrapolation of indicator dilution curves analogous to that used by Jernérus *et al.*[137] for the extrapolation of $P_{CO_2}^z$ in a lung-bag system (see fig. 56), is shown in fig. 23.

In section 4.2 it is shown that indocyanine green, cold isotonic saline- and glucose-solutions and the radioactive isotopes ^{131}I and ^{99m}Tc are the indicators most widely used. Of these, indocyanine green is the indicator of choice as the amount injected can be accurately determined, the concentration in blood can be accurately measured and the number of successive determinations is not limited. In 4.3 the injection system (fig. 24) is described. Using this system the relative error made in the injection of indicator is about 1%; the duration of the injection is about 1 s (fig. 25)[310]. In 4.4 the methods for the detection of indicators in blood are mentioned.

In 4.5 some practical aspects of the influence of recirculation of indicator on the determination of cardiac output are discussed. Special attention is paid to Arkema's[1] extrapolation method (fig. 26 and 27, table 24). It is concluded that Hamilton's semi-logarithmic extrapolation method is the method of choice; however, injection and measuring site should be chosen as close together as possible. In 4.6 several methods for the determination of the area under an indicator dilution curve are discussed. The results of a comparison between these methods are shown in table 29. In 4.7 the derivation of the equations for the calibration of dye dilution curves (4.7.1), of thermodilution curves (4.7.2) and in radiocardiography (4.7.3) are given (equations (108) - (121)). The analogy of the dynamic calibration method[241,242] with the method in which blood samples with known dye concentrations are led through the cuvette, is clearly shown in the equations (112) and (113).

Chapter 5

In section 5.1 some properties of indocyanine green have been discussed. A survey is given in figs. 37-40 and tables 30-32. Indocyanine green has an

absorption spectrum which makes the dye very suitable for use in the dye dilution method (fig. 40); a 1% solution of the dye in distilled water is rather stable for 8 h after preparation (fig. 39). The dye can be sterilized using ethylene oxide without change in optical properties (table 31); after the dye solution has been prepared, it should be stored in the dark (table 32). In 5.2 a linear reflection densitometer for indocyanine green[259] is described. The construction of this apparatus is based on the observation that the reciprocal value of the amount of light reflected by blood in the cuvette is linearly related to the dye concentration in the blood (fig. 41). This relationship is linear up to a concentration of 40 mg $\cdot$ l^{-1} indocyanine green (figs. 49 and 53). The influence of changes in S_{O_2} on the deflection of the densitometer is slight: a change of 5% oxygen saturation corresponds to a deflection which would be caused by an amount of dye of 0.2 mg.l^{-1}; calculation lines obtained with samples of the same blood but with different oxygen saturation are identical (fig. 49).

In 5.3 the dynamic calibration method is compared with the calibration method in which blood samples with known dye concentration are led through the cuvette (*niveau* calibration). Fig. 51 shows the set-up used to obtaine calibration peaks, fig. 47 the apparatus used to prepare blood samples with known dye concentration. Table 36 shows the results of the comparison between both calibration methods; there is no systematic difference, the standard deviation of differences is, however, rather large. It is concluded that both calibration methods are equivalent. However, if accurate calibration is necessary, using the *niveau*-calibration it is not sufficient to determine one point of a calibration line once and using the dynamic calibration, it is not sufficient to make one calibration peak. With the set-up of fig. 51 it is easy to make several calibration peaks in succession, in the beginning and at the end of an experiment. This seems to be the method of choice (fig. 58).

As there is a correlation between the haemoglobin concentration of blood and the slope of the calibration line (figs. 53 and 54; equation (124)), it is possible to calculate the calibration factor y of the dye dilution curve from the haemoglobin concentration of the blood. Table 39 shows the results of a comparison between this calibration method and the conventional calibration methods. A disadvantage of the new calibration method is that the amount of dye injected must be accurately known in units of weight. In 5.4 it is concluded that with the dye dilution method the cardiac output can be determined with a maximal relative error of about 10%.

In section 6.1 results obtained with the linear reflection densitometer have been compared with those obtained with a Waters X-250 transmission densitometer. The cuvettes of both densitometers were connected in tandem. In 4 dogs 108 nearly simultaneous determinations were performed. One of the records is shown in fig. 55. The mean difference between $\dot{Q}(R_0^b/R^b)$ and $\dot{Q}(T)$ expressed as a percentage of $\dot{Q}(T)$ was -0.3%; the standard deviation of the individual differences was 7.1%. Fig. 56 shows the results. The large standard deviation is probably due to the influence of the glucose-solution used to flush the dye solution into the blood on the light reflection as well as the light transmission of blood at the measuring site. This effect of the glucose-solution can be eliminated by injecting more dye meanwhile recording the curve at a lower sensitivity.

In 6.2 results obtained with the dye dilution method (reflection densitometer) are compared with those obtained using the thermodilution method. In 11 dogs 266 nearly simultaneous determinations of cardiac output were performed. The thermodilution curves were obtained with an injection-thermistor catheter, the thermistor being situated in the pulmonary artery[284,285]; glucose-solutions of room temperature were injected into the right atrium. Fig. 55 shows one of the records. The mean difference between $\dot{Q}(td)$ and $\dot{Q}(d)$ expressed as a fraction of $\dot{Q}(d)$ was +6%, the standard deviation of the individual differences 7%. The results are shown in fig. 57.

In 6.3 results of quasi-simultaneous determinations of the dye dilution method with the direct O_2-Fick are communicated (see also chapter 3). Figs. 16, 58 and 59 and table 43 give an adequate survey of the results.

In 6.4 experiments are described in which the cardiac output determined with an electromagnetic flowmeter was compared with the cardiac output determined with the dye dilution method. Two experimental set-ups were used (figs. 61 and 62); in both it was possible to calibrate the electromagnetic flowprobe *in situ.* The results are shown in tables 46 and 47. The large differences found between the results obtained with the dye dilution method and those with the electromagnetic flowmeter are probably due to the velocity profile-dependency of the electromagnetic flow probe used (fig. 63).

Chapter 7

A derivation of the equations used for the calculation of left to right and right to left shunts according to Mook and Zijlstra[185], has been given. With

this method it is possible to calculate $\dot{Q}_p$ and $\dot{Q}_s$ from a single arterial dye dilution curve. Using the ascorbate dilution method[198,199], the shunt blood flow can be measured as a fraction of $\dot{Q}_p$ or $\dot{Q}_s$; when combining the ascorbate dilution method with the thermodilution method[201] it is also possible to determine $\dot{Q}_p$ and $\dot{Q}_s$.