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Abstract—*The indicator-dilution technique is commonly used to determine mean flow estimates. The estimation of instantaneous flow from the shape of an indicator-dilution curve is the objective of this study. Based on a mixing chamber approach to the flow system, a mathematical relationship is derived to reconstruct momentary flow from an indicator-dilution curve. This relationship is verified in a model setup both with only constant flow and with a sinusoidal flow variation superimposed. This method proved to give good flow estimates for limited values of flow parameters. Also, some preliminary experiments were performed in a pulsating flow system simulating heart action. The results were promising although the method proved to be very sensitive to baseline offset.*

Keywords—*Indicator dilution, Instantaneous flow, Mixing chamber model*

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1 Introduction

THE INDICATOR-DILUTION technique is often used in clinical and physiological situations to determine cardiac output estimates (BRANTHWAITE and BRADLEY, 1968; SILOVE *et al.*, 1971). Owing to the nonstationary character of the flow, caused by heart pulsations and ventilation effects, large errors can occur in cardiac output determination when using the technique in these applications. This was concluded from model experiments, theoretical studies (CROPP and BURTON, 1966; BASSINGTHWAIGHTE *et al.*, 1970; VON RETH *et al.*, 1983) and *in vivo* experiments (JANSEN *et al.*, 1979; 1981; SNYDER and POWNER, 1982).

Solutions were proposed by these authors to correct for the mentioned nonstationary effects in the estimation of the mean flow value. The effects of nonstationary flow can be recognised in the shape of the indicator-dilution curve. It is the purpose of the present study to investigate whether information about the instantaneous flow as well as a mean value determination can be obtained from an indicator-dilution curve. Both low-frequency variations (ventilation) and high-frequency variations are aimed at. Until now, determination of variable flow phenomena from indicator-dilution curves has been restricted mainly to beat-to-beat estimates of ventricular outputs and volumes (JARLOV and MYGIND, 1979; JARLOV and LARSEN, 1981). CROPP and BURTON (1966) estimated the instantaneous value of the flow from the concentration recordings after a continuous infusion of indicator. They concluded that the reciprocal of the measured indicator concentration plotted against time gives an acceptable representation of instantaneous flow when the mixing is good and the distance between injection and sampling points is small. Their analysis is not, however, applicable to the bolus-injection method.

We studied the estimation of instantaneous flow with the bolus-injection method by representing the mixing system by ideal mixing chambers in series. The usefulness of this model was tested by analysis of curves either theoretically derived or measured in a hydrodynamical setup.

2 Theory

Modelling indicator transport in a flow system by means of a series of ideal mixing chambers has been described by several investigators (SCHLOSSMACHER *et al.*, 1967; VALENTINUZZI *et al.*, 1972; VON RETH and BOGAARD, 1983; VON RETH, 1984). The flow as a function of time can be derived from the differential equations describing the

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mixing of indicator in a system of N equal ideal mixing chambers in series after a bolus injection of indicator:

$$V \frac{dC_k(t)}{dt} = -F(t)(C_k(t) - C_{k-1}(t)) \quad k = 1 \ldots N \tag{1}$$

where V is the volume of each mixing chamber, C_k is the concentration behind the kth chamber and $F(t)$ is the flow function.

This set of equations can be solved for a known flow function and initial conditions to describe the indicator-dilution curve (SCHLOSSMACHER *et al.*, 1967).

The other way around, it is also possible to derive the flow function $F(t)$ when we start from a measured $C_N(t)$ curve and known initial conditions.

For a bolus injection of indicator (δ-function) in a flow with a zero indicator concentration the initial conditions read:

$$C_1(0) = \frac{m_{inj}}{V} \quad \text{and} \quad C_0(t) = 0 \tag{2}$$

where m_{inj} is the amount of indicator injected.

In our analysis we take the quotient of the first and the last differential equations from eqn. 1.

$$\frac{dC_N(t)/dt}{dC_1(t)/dt} = \frac{C_N(t) - C_{N-1}(t)}{C_1(t)} \tag{3}$$

when

$$\frac{dC_1(t)}{dt} \neq 0 \quad \text{and} \quad C_1(t) \neq 0.$$

Eliminating the time variable gives

$$\frac{dC_N(C_1)}{dC_1} = \frac{C_N(C_1) - C_{N-1}(C_1)}{C_1} \tag{4}$$

which is a standard first-order differential equation. The solution of eqn. 4, taking eqn. 2 into account reads:

$$C_N(C_1) = \frac{1}{(N-1)!} C_1 \left\{ -\ln\left(\frac{C_1}{m_{inj}/V}\right) \right\}^{N-1} \tag{5}$$

To illustrate the use of eqn. 5 we consider the situation with a constant flow F_c, where the (virtual) indicator-dilution curve $C_1(t)$ is given by

$$C_1(t) = \frac{m_{inj}}{V} \exp\left(-\frac{F_c}{V} t\right) \tag{6}$$

Using eqn. 6 in eqn. 5 gives, for constant flow,

$$C_N(t) = \frac{m_{inj}}{V} \frac{1}{(N-1)!} \left(\frac{F_c}{V} t\right)^{N-1} \exp\left(-\frac{F_c}{V} t\right) \tag{7}$$

an equation also found by SCHLOSSMACHER *et al.* (1967), among others.

Flow $F(t)$ can be derived from the set of differential equations of eqn. 1 by rewriting the equation for the first compartment:

$$F(t) = -V \frac{dC_1(t)/dt}{C_1(t)} \tag{8}$$

Both $C_1(t)$ and $dC_1(t)/dt$ can be calculated from the measured $C_N(t)$ and $dC_N(t)/dt$ curves using eqn. 5. This leads to

$$F(t) = -V \frac{dC_N(t)/dt}{C_N(t)} K(t) \tag{9}$$

where

$$K(t) = \left\{ 1 + \left\{ \frac{N-1}{\ln\left(\frac{C_1(t)}{m_{inj}/V}\right)} \right\} \right\}^{-1} \tag{10}$$

When discussing the measurements, we will use the function $Q(t)$ which is determined from

$$Q(t) = K(t) \frac{dC_N(t)/dt}{C_N(t)} \tag{11}$$

This function is related to the flow by

$$F(t) = -VQ(t) \tag{12}$$

3 Method

3.1 *Experimental setup*

The procedure described was tested experimentally in a flow system able to produce a constant flow and sinusoidal modulated flow. The flow system used is described in more detail elsewhere (VON RETH *et al.*, 1983; VON RETH, 1984); here only a synopsis will be given. The system consists basically of two pumps (a constant-flow pump and a plunger pump), a mixing compartment partially filled with glass beads to ensure good indicator mixing, and a tube system. The fluid used was a salt solution in water (0·1 g%). Just before the mixing compartment, injection of a small amount (1 ml) of 0·5 g% salt solution is made. Behind the mixing region, the conductivity was measured using an electrode formed by two stainless-steel rings. The mixing system was characterised by fitting an N-compartment function to a curve, measured with constant flow following the procedure described in VON RETH *et al.* (1983) and VON RETH (1984), resulting in an N-value and a time constant best describing the mixing system.

By the choice of suitable mixing parts (mixing volumes of varying shape, glass beads, tubes), the system could be varied from a system best described as a single mixing chamber to one best described as a series of N compartments ($2 < N < 6$). Simultaneously with the conductivity against time curves, the flow was measured directly with an electromagnetical flowmeter. The indicator injection was pneumatically driven and computer controlled. Under constant flow conditions ($F(t) = F_c$) the reproducibility of measurements and flow analyses was checked. For several values of constant flow, the estimated flow was assessed by comparing the values measured directly and estimations of the flow using eqn. 11.

The sinusoidally varying flow is defined by

$$F(t) = F_m\{1 + A \sin(\omega t + \phi_{inj})\} \tag{13}$$

where F_m is the mean flow, A the relative amplitude of the variation, ω the frequency of the variation and ϕ_{inj} the phase at the moment of injection. With eqn. 12 a function $Q(t)$ is expected that reads:

$$Q(t) = Q_m\{1 + A_q \sin(\omega_q t + \phi_q)\} \tag{14}$$

For these flows, experimental indicator-dilution curves were analysed for several values of F_m, A and ω. The value of $Q(t)$ was calculated from the measured $C(t)$ curves using eqn. 11. The function defined by eqn. 14 was fitted to the measured $Q(t)$ curve by adapting the parameters A_q, ϕ_q, ω_q and Q_m. These parameters were compared with the corresponding parameters of the $F(t)$ function. In all the situations studied, the values of ω_q and ϕ_q were equal to ω and ϕ_{inj} within the accuracy of measurement. The values of

Q_m/F_m and A_q/A were measured as a function of the variable $F(t)$ parameters. The experiments in the one-compartment system were performed for two different volumes of the mixing chamber (107·6 and 139·0 ml).

Finally, some introductory experiments were performed in a pulsating-flow setup, which simulates heart action modulated by respiratory effects. This model consists of an electrically controlled plunger pump, a compliant tube as main blood vessel and an adjustable capillary resistance connected to a buffer volume; for an extensive description we refer to von Reth (1984). Fitting the indicator-dilution curve measured in unmodulated flow yields a description of the model as a three-compartment system. In the experiments, the indicator-dilution curve was analysed and the resulting $Q(t)$ function was compared with the flow function measured directly.

3.2 *Data processing*

According to eqns. 9 and 10, the first derivative of the measured indicator-dilution curve has to be determined to estimate the instantaneous flow. During the analysis, the indicator-concentration signal was filtered by a low-pass filter (Krohn-Hite 3341) before being led to an analogue differentiator. A low-pass filter was inserted to eliminate the disturbances evoked by the differentiator. In a branch parallel to the differentiator, the concentration signal was led through an identical filter to compensate for the time delay in the first filter. A computer (DEC/LSI-11) sampled the concentration signal and its derivative with a sampling frequency of 20 Hz. The virtual indicator-dilution curve after the first mixing compartment $C_1(t)$ was determined by solving eqn. 5 numerically. With eqns. 10 and 11, $Q(t)$ was determined as a function of time. The function $Q(t)$ was compared with the flow function $F(t)$, measured electromagnetically and also sampled at 20 Hz.

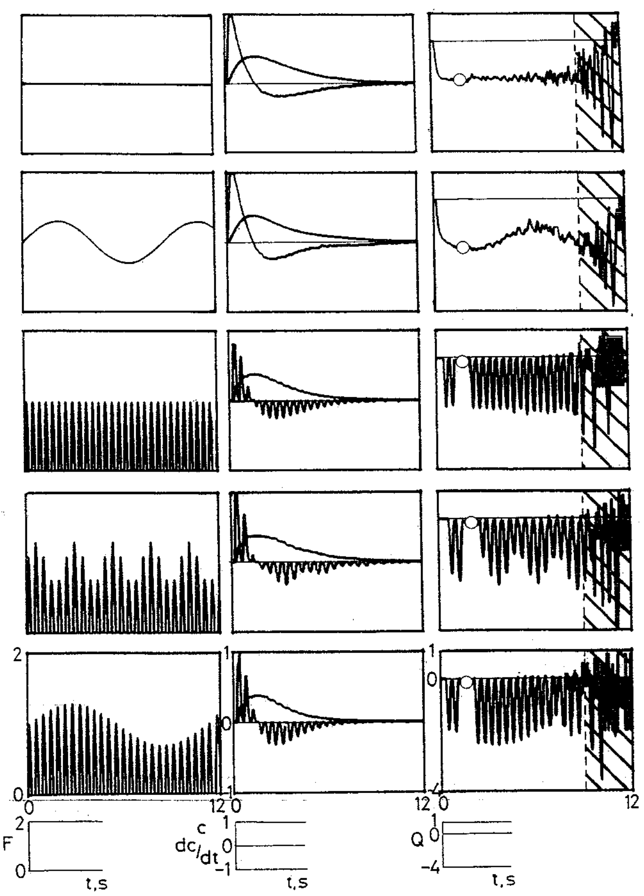

Fig. 1 *Testing the analysis with theoretically derived C(t) curves for various flow situations in a two-compartment model. The graphs on the left show the five different input flow functions, the graphs in the middle present the calculated C(t) curves and their derivatives via analogue differentiation. The right-hand graphs show the Q(t) functions determined by eqn. 11. According to eqn. 12 F(t) ∝ − Q(t). The shaded area and the circle in the Q(t) plots indicate areas where the analysis fails*

4 Results

4.1 *Testing with theoretical curves*

To check the veracity of eqn. 9 and the signal processing procedure, the analysis was performed on curves $C_N(t)$ which were calculated with eqn. 5 and $N = 2$, for five different flow functions. These were the constant flow, the sinusoidal flow, the pulsatile flow with constant amplitude and pulsatile flow with modulated amplitude for two frequencies of modulation. The $C_N(t)$ curves calculated were converted into an analogue signal and recorded on tape. These recordings were led to the differentiator and analysed with the procedure described above (filter frequency 5 Hz). The results are presented in Fig. 1, which shows the input flow functions, the recorded analogue $C_N(t)$ curve and its derivative and the resulting $Q(t)$ functions. In the region where the $C_N(t)$ curve approximates the baseline, the amplitude of the noise level increases rapidly and in the vicinity of the top of the $C_N(t)$ curve, the analysis fails due to inaccuracies in the determination of $C_1(t)$. Except for these parts the $C_N(t)$ curve proves to be useful for determining the instantaneous flow. Modulation effects can be distinguished clearly and even the high-frequency parts of $Q(t)$ compare well with $F(t)$. From this analysis we conclude that instantaneous flow can be estimated except for parts of the curve near the top and where the curve is close to the baseline.

4.2 *Experiments*

For an analysis of time-dependent flow from measured $C(t)$ curves, we restricted ourselves to the useful part of the curve which is described in the theoretical test. The flow variations are expressed by the function $Q(t)$ which can be calculated from eqn. 11. When estimating the absolute flow, an extra measurement will be needed to determine the factor V in eqn. 12, relating $Q(t)$ to $F(t)$. This can be done by comparing the mean value of $Q(t)$ and the mean flow derived from the area under the (flow-weighted) indicator-dilution curve (von Reth, 1984). This is not done in the present analysis.

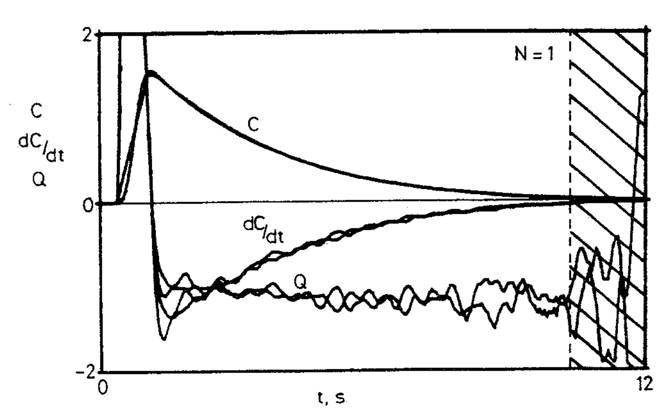

Fig. 2 *Measured curves, derivatives and Q(t) functions in a one-compartment system for constant flow for two successive injections of indicator*

Examples of the analysis with constant flow in a one-compartment system are given in Fig. 2. In this figure, the resulting curves, the derivatives and the calculated $Q(t)$ functions are plotted for two successive injections under identical conditions.

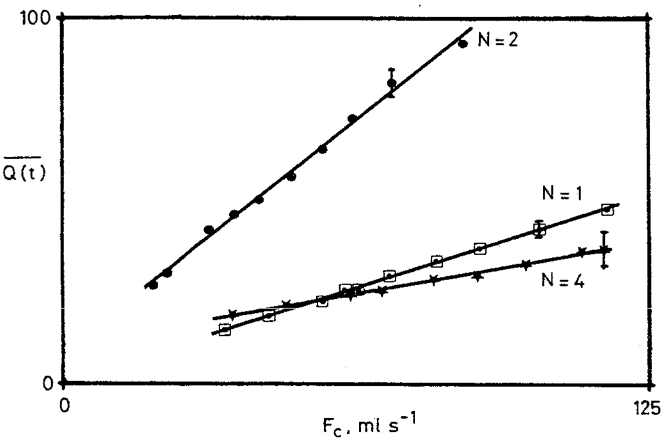

Fig. 3 *Mean $Q(t)$ against flow F_c. Each data plot is the mean value of ten measurements. The standard deviations from the mean are shown with bars*

The relationship between the adjusted flow F_c and the mean value of $Q(t)$ in constant flow is represented graphically in Fig. 3 for a one-, two- and four-compartment system. The $\overline{Q(t)}$ value is linearly related to the flow. The intercept of the extrapolated best-fit line differs significantly from zero in the two- and four-compartment cases, suggesting a higher-order relationship near the origin. According to eqn. 12, the slope of the lines is equal to the volume of one ideal mixing chamber. The calculated total effective volume was approximately 15 per cent smaller than the geometrical volume of the system between the injection and sampling sites; this value varied with the type of mixing system.

One result of an experiment with sinusoidally varying flow is shown in Fig. 4 where the directly measured flow $F(t)$ is presented together with the corresponding indicator-dilution curve, its derivative and the calculated $Q(t)$ function.

The values of Q_m proved to be independent of the frequency and amplitude of the variation and of the phase at the moment of injection. The relationship between Q_m and

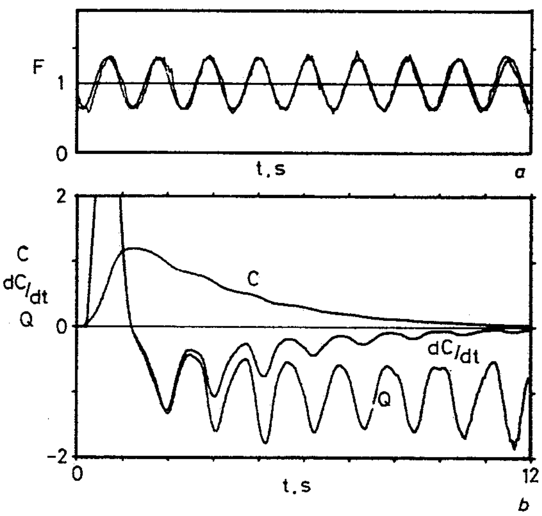

Fig. 4 *Flow estimation in sinusoidally varying flow: (a) flow function; (b) indicator-dilution curve, derivative and $Q(t)$ function*

F_m is linear, analogous to the relationship found in the constant-flow experiments. The quotient A_q/A depended on the values of the mean flow, the relative amplitude, the frequency and the volume of the mixing system. A dimensionless parameter ξ was introduced, representing the quotient of the volume of the fluid that is transferred by the sinusoidal variations and the effective volume of the mixing system; it contained the flow parameters mentioned:

$$\xi = \frac{2\pi A F_m}{\omega N V} \tag{15}$$

The results in the one-compartment case (Fig. 5) and also in the more-compartment systems show that beyond a certain ξ value ($\xi > 0{\cdot}5$), the ratio A_q/A will converge on the expected value of unity.

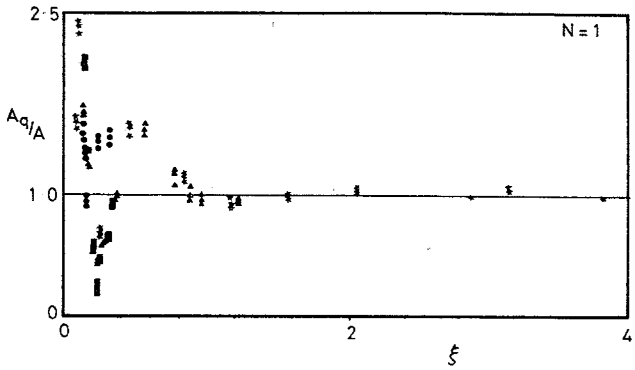

Fig. 5 *A_q/A plotted against ξ for the measurements in the one compartment for sinusoidally varying flow.*
Varied parameters: ▲ = F_m *(V = 108 ml),*
■ = F_m *(V = 139 ml)*
★ = ω, ● = A

Finally, the feasibility of the method was studied using curves measured for pulsatile flow, both modulated and unmodulated. A typical result for unmodulated flow is shown in Fig. 6. The function $Q(t)$ shows a fluctuating pattern with the frequency of the pulsations, but the amplitude of the $Q(t)$ pulses is only constant over a rather small part of the $Q(t)$ curve. Experiments were performed with different amplitudes of $F(t)$ from which it was concluded that the mean of $Q(t)$, for the useful part of the $Q(t)$ curve, shows a linear relationship with the mean of $F(t)$. However, in modulated pulsatile flow the modulation could not be distinguished because there were only a few $Q(t)$ beats in the relevant part of the curve.

5 Discussion

Based on the ideal mixing chamber model a procedure was developed to derive information on momentary flow from an indicator-dilution curve obtained after a bolus injection of indicator. Cropp and Burton (1966) reported a procedure, estimating instantaneous flow from the recording of the reciprocal of a constant-infusion indicator-dilution curve, with restrictions for the distance between injection and detection points. Their analysis was not applicable to the bolus-injection method. Cassot *et al.* (1978) indicated that, with their description of indicator-dilution curves, based on a dispersion theory, evaluation of flow dynamics might be possible.

Our analysis is based on the N-compartment model and comprises analogue differentiation of the measured curve and numerical deduction of the virtual indicator-dilution curve behind the first mixing chamber. Theoretically, the procedure was tested for various flow functions. Except for some parts at the vicinity of the top and near the baseline, the indicator-dilution curve proved suitable for the flow analysis.

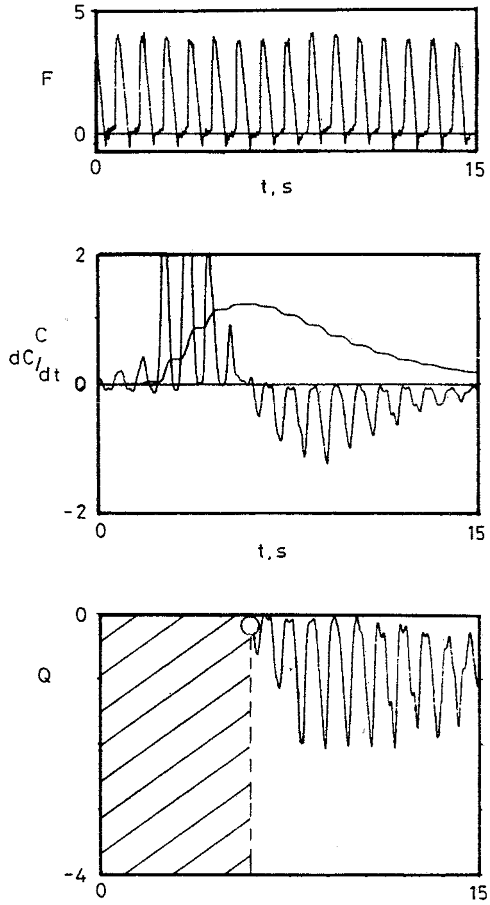

Fig. 6 *Analysis of a curve measured in an unmodulated pulsating flow of a physical flow system. Only the descending limb is used*

The results in a constant flow setup showed a linear relationship between $\overline{Q(t)}$ and F_c in the one-compartment system. For the two- and four-compartment curves an intercept was observed when linear regression was applied, for which theory does not account. This may be caused by more and more asymmetrical curves when the flow decreases, which implies that for decreasing flow the number of compartments describing the mixing system tends to unity. This leads to nonlinearity in the relationship for small flow values.

Measurements in sinusoidal flows with both high-frequency and low-frequency variations with respect to indicator passage time were performed. From these measurements it can be concluded that frequency and phase of the flow can be derived accurately from $Q(t)$. According to the measurements for constant flow, Q_m is related to F_m linearly and is not dependent on other flow parameters. The parameter A_q is linearly related to A, but the quotient A_q/A, however, depends on the mean flow value, the frequency of variation and on the volume of the mixing system. This is expressed by the relationship of A_q/A with ξ.

Testing the analysis in a physical model with pulsating flow showed the limitations of this procedure: for high-frequency pulsations associated with small ξ values, the amplitude could be miscalculated, as is shown in Fig. 5. For low-frequency pulsations, the amplitude is fairly accurate, but only a few pulsations will occur during the passage of a curve when the values of flow and mixing parameters are chosen in accordance with physiological data. Furthermore, the position of the baseline seemed to be of great influence. This effect is illustrated in Fig. 7, where a theoretical indicator-dilution curve for constant flow is plotted with its analytically determined derivative and $Q(t)$ function. In the situation marked $_1$ the baseline of the indicator-dilution curve is zero and $Q_1(t)$ is a straight line representing the constant flow. In situation $_2$ the curve is offset by 2 per cent of the maximum value. The shift in the $C(t)$ curve is barely visible and its derivative is identical to the one in $_1$. Function $Q_2(t)$ is constant and equal to $Q_1(t)$ for the first part of the curve, but it deviates increasingly in the descending part.

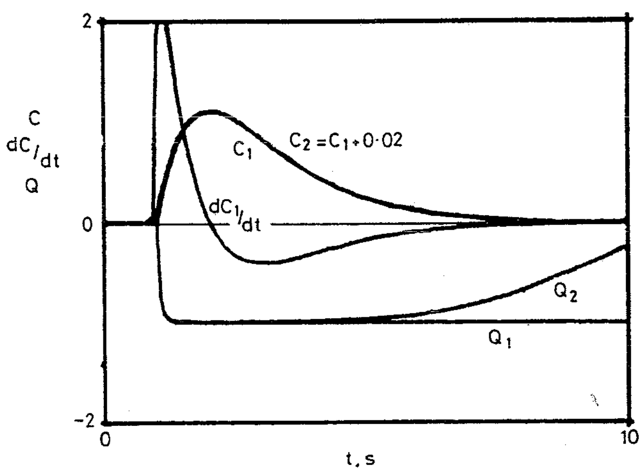

Fig. 7 *Effect of baseline offset on* $Q(t)$

In conclusion, it is stated that the analysis of instantaneous flow holds for the constant flow case and, with restrictions, for the sinusoidal flow case. In pulsatile flow, the results for the unmodulated case are promising. The proposed analysis should be developed and tested in more detail and, furthermore, an evaluation in the *in vivo* practice is needed. Attention must be given to the time constant of the indicator measuring device which must be sufficiently small to allow for the measurement of high-frequency flow variations via the indicator-dilution curve.

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Dr Ir E. A. von Reth studied physics at the Eindhoven University of Technology and graduated in 1978. In 1983 he received his Ph.D. with a thesis 'Assessment of the indicator-dilution method in non-stationary flow'. At present he is working with Philips International BV, Medical Systems Division, in the application of new radiological methods and equipment in clinical practice.

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Dr Ir A. A. van Steenhoven received his Doctor of Engineering degree in 1979 from Eindhoven University of Technology, The Netherlands, where he is staff member in the department of Mechanical Engineering. His primary interest is the application of fluid dynamics on the cardiovascular system.

Professor J. A. Poulis is lecturer at the department of Physics of the Eindhoven University of Technology. His research area is the analysis of physical measuring methods, especially in the biomedical field.

Professor A. Versprille is a full professor in clinical respiratory physiology and head of the research laboratory of the Department of Pulmonary Diseases, Erasmus University, Rotterdam and head of the pulmonary laboratory, University Hospital 'Dijkzigt'. The field of mechanical ventilation and the development of diagnostic and therapeutic methods as a spinoff of this basic reserach are his main interests.