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SIMULATION OF THE CARDIOPULMONARY CIRCULATION: An Experiment in Reactor Analysis with Medical Applications

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THE INDICATOR DILUTION technique is a very important diagnostic method for the calculation of cardiac output (i.e. the blood flow rate), cardiopulmonary volumes and mean transit times, as well as for the detection of circulatory diseases and abnormalities [1, 2]. As this technique is based almost exclusively on the principles of chemical reactor analysis, it represents a very suitable experimental topic for students in chemical engineering and bioengineering, and is particularly valid for the growing number of those who are preparing themselves for future medical studies. The experiment described herein has been one of the projects in the senior laboratory courses offered by the Department of Chemical Engineering and Applied Chemistry of Columbia University.

Use of tracers has been a very common method in the study of flow reactors. Internal and exit age distribution functions [3] in chemical reactors are calculated by analyzing the response curve to a tracer input signal. As the heart chambers are analogous to stirred tank reactors [4, 5], the principles of reactor analysis can be employed in the study of the human circulation.

Figure 1 is a simple representation of the heart. Its right chambers are essentially a mixing vessel that pumps blood into the lungs. Since the pulmonary circulation is an extended capillary system, flow occurs with little mixing. The left side of the heart is analogous to the right; it, too, is a mixing chamber whose purpose is to force the blood out into the body (systemic circulation). A bolus of indicator (a dye, for example) is injected into one point of the system and the time dependent detection of the tracer is made at a second point. From these data, the volumetric flow rate and the volume of the system between the injection and sampling points can be determined.

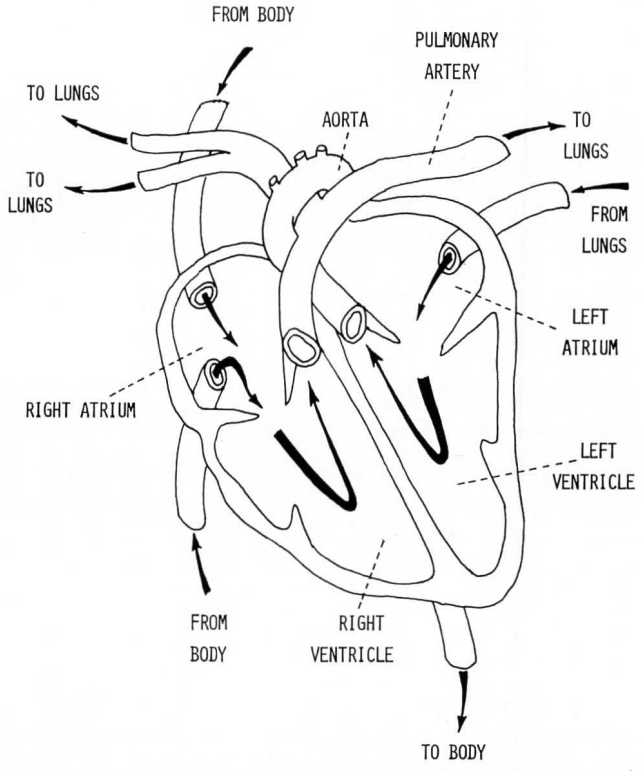


FIGURE 1. Blood flow patterns in the heart chambers.

Current clinical indicator dilution practice is based upon the Stewart-Hamilton formulation [6] which treats the vessel wherein the tracer is injected as an ideal stirred tank. The indicator is usually a radionuclide such as Tc^{99m} or I^{131}, although dyes are sometimes used. A more suitable tracer for a laboratory experiment is a soluble salt (e.g. KCl) so that continuous conductivity

measurements can be made at appropriate positions within the circulatory reactor model.

THEORY

THERE EXIST TWO types of continuous ideal chemical reactors, the Continuous Flow Stirred Tank Reactor (CFSTR) and the Plug Flow Tubular Reactor (PFTR). The first of these is a vessel in which perfect mixing assures uniform concentration in all parts of the tank; this also accounts for the concentration of the outflow stream being identical to that of the reactor contents. In the absence of chemical reaction, the ideal CFSTR is simply a vessel for perfect mixing of a number of materials.

The ideal PFTR represents the opposite end of the spectrum. It is commonly a tube in which the concentration is uniform at each radial cross section, but with no mixing taking place in the axial direction. The fluid traverses the tube with a flat velocity profile; thus, the necessary and sufficient condition for ideal plug flow is that all flow elements have the same residence times in the reactor. For this reason, in the absence of chemical reaction, the PFTR behaves as a delay function within a flow system.

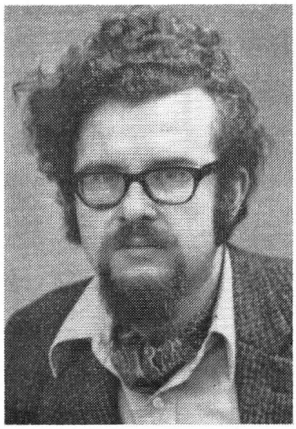
The response of ideal reactors to different inputs is extensively covered in the literature [3, 7]. When an impulse injection of a tracer is made into an ideal CFSTR, the concentration in the effluent decays exponentially. Then, the flow rate, F, is given by the formula

$$F = \frac{I}{\int_0^\infty C(t)\,dt}, \qquad (1)$$

where I is the amount of tracer injected and C(t) is the time-varying concentration of indicator in the outflow stream. The denominator of this expression represents the total area under the concentration-time curve and can be evaluated analytically, graphically, or numerically [8, 9].

The mean transit time, $\bar{t}$, of tracer in a vessel

As the heart chambers are analogous to stirred tank reactors, the principles of reactor analysis can be employed in the study of human circulation.



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is the average of the individual residence times of all indicator particles. Thus,

$$\bar{t} = \frac{\int_0^\infty t \cdot C(t)\,dt}{\int_0^\infty C(t)\,dt}. \qquad (2)$$

Once the flow rate and mean residence time in a vessel have been determined, its volume is found by multiplying these two quantities:

$$V = F \cdot \bar{t} \qquad (3)$$

To apply this analysis to the study of the human circulation, a rapid injection of tracer is made into the right heart. This would yield the arterial dilution curve of Figure 2a or the precordial dilution curve of Figure 2b, depending upon the method of sampling. If samples are obtained directly from an artery subsequent to the right heart, indicator concentration will rise sharply after injection and then decrease as the tracer is washed away by the blood flow yielding

the general shape seen in Figure 2a. If the injection is practically instantaneous and the right heart operates as a CFSTR, then, on the basis of the above analysis of ideal reactors, the upstroke of the arterial dilution curve should be vertical and the decay exponential (see e.g. Figure 4a).

When a radioisotopic indicator is used, the precordial dilution shape of Figure 2b is obtained.

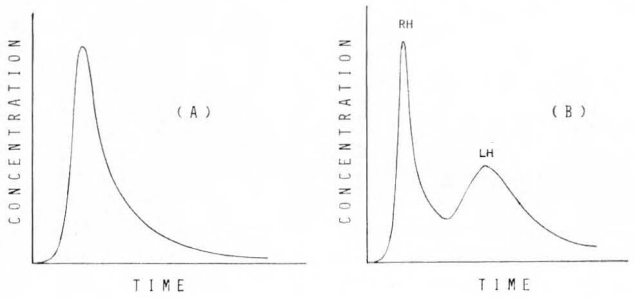

FIGURE 2. Generalized arterial (a) and precordial (b) dilution curves. RH: right heart peak; LH: left heart peak.

Again, a right heart peak and decay are seen immediately after injection. However, since the left heart is also within the field of the gamma ray detector, a second peak will appear as the radioactive particles enter the left heart after having traversed the pulmonary circulation. This peak will be lower than the right heart peak because of the substantial dilution of tracer during its flow through the cardiopulmonary circulation, and will also decay as the tracer particles enter the systemic blood pool.

Theoretical analyses of the indicator dilution technique are described in detail in the literature [10, 11] and the applicability of the previously discussed chemical reactor theory to indicator dilution practice [12] and to subsequent investigation of the pulmonary circulation [13] has been analyzed. Application of chemical reactor analysis requires the following assumptions:

- **The tracer used should have rheological properties similar to those of whole blood.**
- **The circulation should contain no stagnant pools [14].**
- **The heart chambers should function as CFSTR's [4, 5].**
- **Impulse injections must be used [15].**

The above references state and discuss the validity of their respective assumptions.

EXPERIMENTAL

THE GENERAL LAYOUT of the apparatus is shown in Figure 3. An open system is preferable to a closed one from the experimental point of view because it does not require flushing out of the indicator after each run, or subtraction of the initial tracer concentration. A further advantage of this arrangement is that the use of a pump is not necessary for fluid flow.

Continuous Flow Stirred Tank Reactors are used to model the two heart chambers [4, 5]. These should ideally be made of a transparent plastic (e.g. poly(methyl methacrylate)) to permit close observation of fluid flow through them. Their shape should be cylindrical to eliminate stagnant pockets, and their diameter and height should be of comparable dimensions. To maximize mixing, the inflow and outflow tubes should be placed tangentially to the curved cylinder surface at its bottom and top, respectively. The volume of the right and left heart models should be the same as in the average human circulatory system (130 to 150 cc).

The pulmonary circulation is also modelled by a transparent cylinder of the same material as the right and left heart. Lovinger [13] has shown that pulmonary circulation behaves essentially as a chemical reactor containing ca. 75% plug flow regions and 25% mixing ones. This is consistent with the actual physiological system because it is expected that practically no mixing will be taking place in the capillaries which would instead provide most of the delay during pulmonary flow; however, substantial mixing should be taking place in the large arteries and veins and at all junctions. In practice, it was found that a long cylinder, ca. 1.5″ in diameter and 14″ long, will have the average pulmonary volume (400 cc) and provide the above percentages of mixing and plug flow. Mixing will obviously be concentrated at the entrance and exit regions, with plug flow in between. A closer approximation to plug flow is obtained when this cylinder is placed vertically since

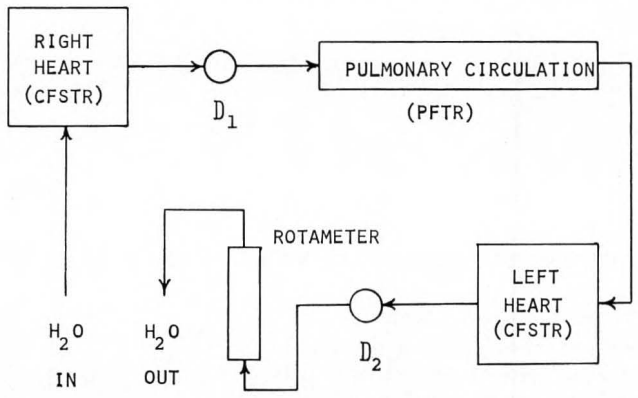

FIGURE 3. Flow diagram of the experimental apparatus. CFSTR: Continuous Flow Stirred Tank Reactor; PFTR: Plug Flow Tubular Reactor.

If the injection is practically instantaneous and the right heart operates as a CFSTR, then, on the basis of the above analysis of ideal reactors, the upstroke of the arterial dilution curve should be vertical and the decay exponential.

the force of gravity will tend to flatten the velocity profile.

These three vessels are connected in series by use of flexible transparent tubing (e.g. soft poly (vinyl chloride)). The total length of connective tubing should be minimized, and the volume of the segments between the pulmonary circulation and the two heart chambers should be counted as part of the pulmonary blood volume.

The circulating fluid used is ordinary tap water, whose rheological properties are similar to those of blood. Its flow rate is controlled by a needle valve and measured by a rotameter. The indicator is 4N KCl, although lower concentrations can be used if the chart recorder has a sensitivity greater than 10 mV full scale. Injections are made by use of a syringe attached to a valve and needle. The needles are actually put permanently through the walls of the tubing at appropriate positions ahead of the right and left heart. They are held in place by use of silicone rubber and contain stopcocks which are ordinarily closed so that no water escapes through them due to the flow pressure.

Two conductivity cells are installed in-line after the right and left heart vessels (points D_1 and D_2 in Figure 3) to monitor the concentration of KCl. Each consists of two platinized rods, 0.5 mm in diameter, extending 2 mm into the stream, and is connected through a switch to a specific conductance meter (Beckman Instruments, Inc.) having a scale of 50 micromhos/cm. This in turn is attached to a chart recorder (Bausch & Lomb, Inc.) which provides continuous curves of d.c. voltage versus time. To minimize the amount of tracer injected, as low a scale as possible of voltage should be used (preferably less than 10 mV full scale). Chart speed can be varied; the speed used in our experiments is 5 inches/min.

EXPERIMENTAL PROCEDURE

ONCE THE APPARATUS is set up and working properly, the actual experimental procedure should require no more than one laboratory period of five hours by a team of at least two students or the equivalent. The rotameter is calibrated first by use of a volumetric cylinder and a timer; a calibration curve of rotameter reading versus flow rate in lit/min should be constructed to cover the entire spectrum of cardiac outputs obtainable, i.e. from 1 lit/min to 10 lit/min. Next, a calibration curve relating recorder voltage to indicator concentration should be constructed by use of standard solutions of KCl.

After these two curves are obtained, the actual indicator dilution procedure can take place by establishing a constant flow rate and injecting a minimum (preferably less than 3 cc) of KCl solution as rapidly as possible. Injections should be made ahead of each vessel (equivalent to venous injection in humans) or directly into the right heart by use of a catheter. Either of the two conductivity cells D_1 and D_2 should be attached to the recorder, so that arterial dilution curves similar to those shown in Figure 4 will then be obtained. For actual calculations, it is best to follow the usual medical practice by injecting directly into the right heart and sampling at D_1. The same procedure should be repeated at different flow rates and with variation of injection sites and types. From these data, one is able to investigate the effect of flow rate, injection duration, and injection and sampling positions upon the accuracy of calculations.

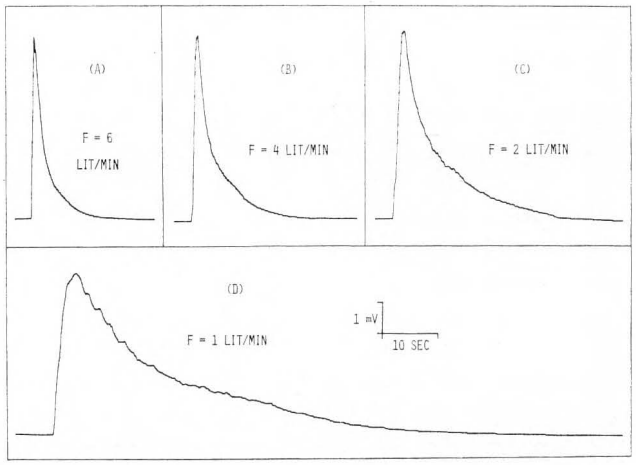

FIGURE 4. Indicator dilution curves obtained for various flow rates from the circulatory model. Tracer injected into the right heart by use of a catheter and detected at point D_1 in Figure 3.

Calculations: By use of indicator dilution curves obtained as above, and of Equation (1),

the cardiac output can be calculated and compared to the actual flow rate given by the rotameter calibration curve. Similarly, mean residence times in circulatory segments can be determined from Equation (2). Equation (3) can then be employed in the calculation of the various volumes between injection and detection points which should be compared to the actual volumes in the circulatory model. Means and standard deviations of cardiac output and right heart volumes might also be determined for the runs at each flow rate. Finally, the downslopes of the dilution curves obtained should be plotted in semilogarithmic coordinates to check linearity at the various flow rates.

RESULTS AND DISCUSSION

WHEN FLOW RATES between 3 and 6 lit/min are employed, all parameters should be computed to an accuracy of better than 5%, provided that injections were made rapidly directly into the right heart. Obviously, slower injections or those that were made in the tubing ahead of the above vessels will cause higher deviations from the true values of cardiac output because the impulse injection and the ideal mixing assumptions will no longer be completely valid. The same tendency in the results will also be observed in lower flow rates since the turbulence created in the two heart vessels will not be adequate to assure perfect mixing. This may also result in the formation of stagnant pockets which will provide erroneously low values for the heart volumes. Very high flow rates (above 7 lit/min) imply minimal tracer residence times in the heart chambers; thus, if the response of the conductance meter or chart recorder is not sufficiently fast, inaccuracies may again be obtained. The mixing effects in the various vessels can be qualitatively observed if a colored dye (e.g. Rhodamine) is added to the KCl solution.

A significant measure of the rapidity of injection and of the degree of mixing within the heart chambers is provided by the shape of the arterial dilution curves. At the higher flow rates (above 3 lit/min) the initial upstroke is almost vertical and the downstroke approaches very closely a theoretical exponential decay (see Figures 4a and 4b). Deviations from this behavior are seen at lower cardiac outputs (Figures 4c and 4d). The students will be able to see this tendency more descriptively if the downstrokes of the dilution curve at various flow rates are replotted in semilogarithmic coordinates, in which an exponential decay appears as a straight line. Consequently, least squares curve fitting procedures can be used to test deviations from this behavior.

The nature of these calculations (i.e. repeated integrations and least squares curve fittings) makes use of computer programming particularly attractive. Subroutines for these numerical computations are available in the literature [8, 9] and could be used by the students, who would only have to provide the values of the dependent and independent variables when calling up the appropriate subprogram. A complete computer program that calculates cardiac output, mean residence times and circulatory volumes has been reported in the literature [16]. Composition of such a complete computer program may also be undertaken by a team of students as a term project.

Another suitable project may involve the investigation and explanation of the effects of circulatory diseases and abnormalities (e.g. arteriovenous shunts, mitral and aortic stenoses, "blue baby disease") on the indicator dilution curves. In most actual medical cases, these anomalies are detected and quantified by use of precisely this method, and numerous references are available in the literature [e.g. 12, 17]. These circulatory abnormalities can be very easily studied on the model by simply adding flow connections between the appropriate points for each case.

ACKNOWLEDGEMENT

The authors wish to thank Professor Elmer L. Gaden, Jr., and Mr. Frank Lech for their part in the design of the experiment. □

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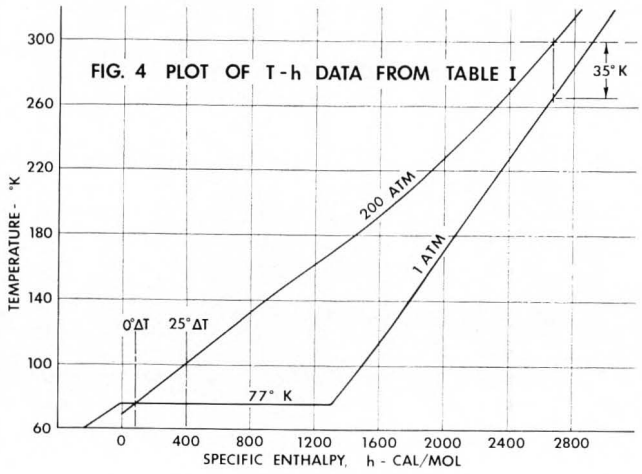

cold end temperatures move to the right on Fig. 4, with the 25K case being shown. Interestingly, if the area is further decreased to give more than a 35K difference, then the minimum Δt switches back to the warm end.

The curves on Fig. 4 also should indicate to the student that to size such a heat exchanger, one must break it up into the evaporating portion and the heating portion to allow the use of log-mean temperature differences, since the stream heat capacity abruptly changes. Actually, one must also estimate the film coefficients, as these are different in the two sections, and constant film coefficients, as well as heat capacities, are assumed when the log-mean relationship is derived. With no phase change, but with non-linear cooling curves (variable heat capacity), one should size a heat exchanger by point-to-point integration rather than the use of a log-mean driving force.

CONCLUSIONS

THE GRADUATING chemical engineer should go out on the job with a clear understanding of the thermal equilibrium case in heat exchangers (for infinite areas), for elegant heat transfer theory and correlations are useless if the basic equilibrium case is not even understood.

The use of the J-T Demonstrator is considered a classical way of showing the floating nature of the pinch-point, which shows up in many heat exchangers encountered on the job, when changes of phase or flow rates are encountered. □

ACKNOWLEDGEMENT

I wish to thank Mr. Robert B. Currie, Principal Development Engineer, Air Products and Chemicals, Incorporated, for reviewing this paper. He was responsible for the excellent hardware design on the demonstrator.

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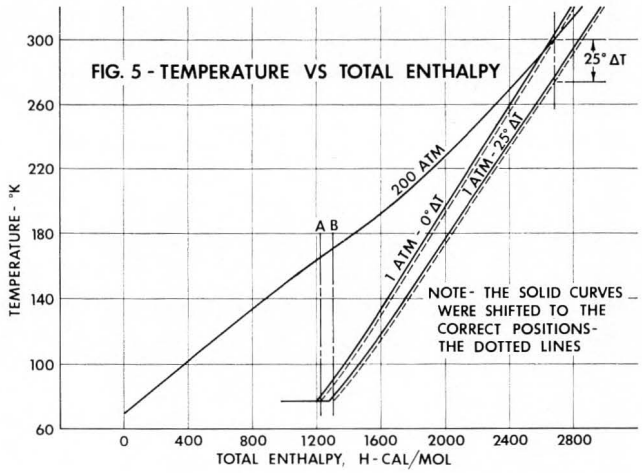

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