ARTERIAL BLOOD FLOW PATTERNS IN HUMAN SUBJECTS AND THEIR EFFECT ON INDICATOR DILUTION CURVES FROM VARIOUS ARTERIAL SITES*

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Indicator dilution curves obtained from various systemic arterial sampling sites are commonly used for analysis of blood flow, cardiac shunts and valvular regurgitation, and for study of segments of the blood volume. It is generally assumed that the contour of such curves is largely determined by the passage and dilution of the indicator in the central circulation and that changes occurring during arterial passage are minor and predictable on the basis of the expected velocity of arterial blood flow and the distances of the commonly used sampling sites from the aortic root. Although it is accepted that quantification of blood flow is unaffected by changes in curve contour so long as the first circulation of indicator can be identified, the estimation of other parameters available from curve analysis may be significantly influenced by the validity of the above assumption. Beard, Wood and Clagett (1) and Fox, Sutterer and Wood (2) have demonstrated considerable differences in contour as well as appearance time of curves obtained from the femoral (FA), radial (RA) and dorsalis pedis arteries. The first study showed delay in the FA components in coarctation of the aorta as compared with the RA curve, whereas the latter study noted delay and skewing of the RA or pedal curve as compared with the FA curve. The FA curves were similar in contour to the abdominal aortic curves in normal subjects. During preliminary studies of an investigation which attempted to quantitate valvular regurgitation by comparison of indicator dilution curves recorded simultaneously from the pulmonary artery (PA) and a systemic artery, we noted that in normal subjects only FA curves consistently resembled the PA curve while those recorded from the brachial artery (BA), or RA frequently showed unpredictable deviations in curve parameters.

Although these studies clearly indicate that the sampling site as well as the sampling system (3-6) play an important role in the parameters of dilution curves, it is not clear whether the effects of arterial passage are a predictable characteristic in each arterial system and are constant from subject to subject and from moment to moment, or whether capricious effects occur which are related to spontaneous or reflex local disturbances, possibly produced by the sampling technique.

The present study was undertaken in an attempt to define the extent of variation in curves as obtained from commonly employed arterial sites and to examine the possible mechanism for distortion or skewing of the curves. The results of human studies led to the parallel investigation in a hydraulic analog system having three characteristics considered most important in determining the presence and extent of curve alteration: pulsatile flow, a branched elastic system, and variable efflux resistances. Although the effects on a dilution curve of constant flow through rigid tubing are well known (3-6), little evidence exists as to the pulsatile flow through a branched elastic system encountered in man.

METHODS

Human studies. Studies were carried out in 12 human subjects in the resting state during the course of venous cardiac catheterization. Simultaneous FA and BA curves were obtained following right heart or venous injection of T-1824 or indocyanine green in 4 normal subjects. In 3 others, simultaneous RA and FA curves were obtained (Table I, Subjects 1 through 7). Three patients with coarctation of the aorta were examined: one with minimal narrowing showing only alteration of the central pressure slope (Patient 8), and two with evidence of severe constriction of the aorta and well developed collateral circulation (Patients 9 and 10). An-
of emergency medicine. The medical records showed that the patient had a history of hypertension, diabetes, and renal failure. The patient was admitted to the intensive care unit (ICU) for further evaluation and management.

2. Patient 2: A 45-year-old male was admitted to the ICU with a diagnosis of acute myocardial infarction (AMI). He presented with chest pain, shortness of breath, and diaphoresis. The patient's medical history included a previous MI and coronary artery bypass graft surgery (CABG) 5 years prior. The patient was treated with aspirin, heparin, and a beta-blocker and was placed on a telemetry monitor.

3. Patient 3: A 72-year-old female was admitted to the ICU for postoperative monitoring after undergoing a left hemicolectomy for sigmoid colon cancer. The patient had a history of ankylosing spondylitis and a pacemaker. On postoperative day 2, the patient developed respiratory distress and was subsequently intubated and placed on mechanical ventilation.

4. Patient 4: A 50-year-old male was admitted to the ICU for treatment of severe sepsis caused by Escherichia coli (E. coli) bacteremia. The patient had a history of end-stage renal disease and was on dialysis. He presents with fever, hypotension, and respiratory distress.

5. Patient 5: A 60-year-old female was admitted to the ICU with a diagnosis of pulmonary embolism (PE). She had a history of chronic obstructive pulmonary disease (COPD) and thrombophilia. The patient presented with chest pain, shortness of breath, and hypoxia. She was treated with anticoagulation and placed on a low-flow oxygen delivery system.

6. Patient 6: A 75-year-old male was admitted to the ICU with a diagnosis of acute respiratory distress syndrome (ARDS). He had a history of chronic obstructive pulmonary disease (COPD) and emphysema. The patient presented with severe hypoxia and respiratory failure.

7. Patient 7: A 42-year-old female was admitted to the ICU with a diagnosis of severe sepsis caused by Staphylococcus aureus (S. aureus) bacteremia. She had a history of obesity and diabetes. The patient presented with fever, hypotension, and respiratory distress.

8. Patient 8: A 65-year-old male was admitted to the ICU with a diagnosis of acute pancreatitis. He had a history of alcohol abuse and chronic pancreatitis. The patient presented with abdominal pain, nausea, and vomiting.

9. Patient 9: A 55-year-old female was admitted to the ICU with a diagnosis of acute compartment syndrome of the leg. She had a history of severe lower extremity injury in a motor vehicle accident. The patient presented with severe pain, swelling, and neurovascular compromise.

10. Patient 10: A 38-year-old male was admitted to the ICU with a diagnosis of severe traumatic brain injury (TBI). He had a history of substance abuse and was involved in a high-speed motor vehicle accident. The patient presented with a Glasgow Coma Scale (GCS) score of 3 and was intubated and placed on mechanical ventilation.

11. Patient 11: A 60-year-old female was admitted to the ICU with a diagnosis of septic shock caused by Staphylococcus aureus (S. aureus) bacteremia. She had a history of diabetes and chronic renal failure. The patient presented with fever, hypotension, and respiratory distress.

12. Patient 12: A 50-year-old male was admitted to the ICU with a diagnosis of acute lymphoblastic leukemia (ALL). He had a history of chemotherapy-induced bone marrow suppression. The patient presented with fever, neutropenia, and sepsis.

In conclusion, the ICU stay of each patient was managed with a multidisciplinary approach involving medical, surgical, and nursing teams to provide optimal care and improve outcomes. The challenges faced by these patients underscore the importance of early identification and prompt intervention to prevent complications and improve survival.

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ditions, from 16 to 20 ml. The distal ends of the two branches of tubing could be controlled by screw clamps to provide variable outflow resistances. Indicator was injected proximal to the pump. The latter provided adequate mixing. Dilution curves were obtained through short no. 20 needles connected to direct recording cuvet oximeters. Sampling was accomplished by the paired sampling syringes mentioned previously (3). The rate of sampling at all times was less than 5 per cent of the flow through the model. The model was intended to closely simulate the relative capacity of the arterial tree and the flow rate through it. The following paragraph describes the manner in which local alterations in flow were simulated.

The following experimental conditions were set up to test their influence on the contour of a dilution curve: a) sampling from two branches having equal flow, but equal or unequal volume; b) sampling from two branches having unequal flow, accomplished by changing outflow resistance of one branch only; c) sampling from proximal and distal segments of one branch having increased outflow resistance; d) sampling from a nonexpansile system made so by lowering outflow resistance in both branches; e) sampling from both branches with elevated, but slightly unequal, outflow resistances.

The failure of the galvanometer beam to return to the baseline after curve inscription deserves mention. It was noted that the polyethylene tubing, leading water and T-1824 dye through the recording cuvet, would remain faintly tinted with blue color long after the effluent was

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**FIG. 1.** A characteristic set of curves from a normal male (Subject 1, Table I) showing fairly extreme variation between BA and FA curves. Curves are extrapolated to equal concentrations. B. Simultaneous curves from the FA and RA following PA injection. Recordings were made using cuvet densitometers sensitive to indocyanine green. The variation of the RA curve from the FA curve is qualitatively the same as the variation of the BA curve from the FA curve in 1A.
colorless. We conclude that loose binding between the dye and plastic occurred with a significant effect only at low concentration. We, therefore, doubt the accuracy of the downslope at lower concentrations and have used the segment of the curve shortly after the peak for comparative purposes.

RESULTS

1. Comparison of human curves obtained simultaneously from two arteries. As demonstrated in Figures 1, 2 and 3, considerable variability is encountered when two curves are recorded simultaneously from various arterial sites following single venous or right heart injection.

The measured parameters of paired curves are listed in Table I. There is frequently not only delayed appearance, \( t_d \), of dye at the BA or RA when compared with the FA, but in addition the curve is skewed by further delay in the peak concentration time, \( t_p \), and prolongation of the passage time, \( t_d-t_s \) (Subjects 1, 2, 5 and 6). These findings agree in general with those of Fox, Sutterer and Wood (2), but there is not always significant alteration of the BA curves (Subjects 3, 4, 8 and 12) and the RA curve may be delayed without other alteration (Subject 7). Examination of the pair of curves in Figure 1A shows that the delay in \( t_d \) is about 2.3 seconds, the delay in \( t_p \) 3.5 seconds and the increase in \( t_d-t_s \) is even greater, 5 seconds. Thus, the first appearing dye is delayed at the BA site, but not so much as is the dye par-

![Diagram](http://www.jci.org)
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Equal length, diameter, and flow

Unequal length, diameter, and flow

Distal short

Distal long

FIG. 5. Two successive stroke volumes from a dilution curve, each stroke a rather homogeneous "step function" of concentration. The shaded areas indicate that the mixing length is short compared to the distance over which concentration tends to be constant. This concept would explain the finding of nearly constant contour of curves from various portions of a system where U/F ratios were equal in the two branches. Below, representative curves from such a system are shown.

ticle with average transit time, \( t \), and even less than the particles near \( t_a \). Figure 1B, recorded with more rapidly responding cuvet densitometers from the FA and RA, shows similar findings. The cases included in Table I represent all possible combinations of FA and BA and RA relationships: a) the common occurrence of delayed appearance and skewness of the BA with respect to the FA (Subject 1 and 2); b) no significant difference between FA and BA curves (Subjects 3, 4, 8 and 12); c) delay in onset, \( t_a \), of the RA curves with or without variation of contour (Subjects 5, 6 and 7); d) reversal of usual findings in severe coarctation (Subjects 9 and 10) and in abdominal aortic aneurysm (Subject 11).

2. Cinefluorex studies. In all FA studies including those of three subjects with mild aortic regurgitation, Hypaque, injected slowly at 1 ml per second, was carried distally without visible diastolic retrograde movement. During repeated studies, or if Hypaque was injected at a faster rate for 8 to 10 seconds, a variable degree of retrograde movement, never more than 3 to 5 cm, was apparent in diastole. There was always rapid clearance of injectate from the site.

In the three FA studies with cuff occlusion of the arterial flow just above the knee, striking retrograde flow of Hypaque was seen as far proximal as the aortic bifurcation. Subsequent injections with the cuff released showed the relationships seen in the control period.

Brachial artery injections revealed a more variable pattern. In one patient there was no visible retrograde movement. In two remaining normal
subjects, there was a variable diastolic retrograde movement of injectate with slow clearing of indicator after cessation of injection. In one normal subject, a brief rapid injection of a small volume resulted in retrograde flow so striking that the subclavian artery was opacified and, although radial pulse was palpable, washout time was prolonged to 18 seconds after cessation of injection.

3. Model studies. The outcome of Studies 1 and 2 above suggested the simple branched elastic model (Figure 4) with pulsatile flow and the variations of the volume-flow relations described above. When equal flow occurs through equal volumes of the pulsatile system, the curves obtained from each branch are identical in all parameters. When the volumes to be traversed are unequal but the flow rates are identical, the similarity of the two curves is maintained, but of course the distal curve has delayed inscription (Figure 5). Thus, differences in volume contained in the two branches of the system do not significantly change the contour of the curves. However, a disproportional decrease in flow of one branch ("vasoconstriction"), with volume, elasticity and stroke volume kept constant, shows that, in addition to the expected delay in the appearance time, the peak concentration time and the extrapolated passage time are further significantly delayed (Figure 6). In fact, when compared to the delay in \( t_a \), \( t_p \) and \( t_d \) show even greater "smearing," i.e., they demonstrate progressive delay when compared to the same measurement of the branch of the model that had normal outflow resistance. This same relative difference between \( t_a \), \( t_p \) and \( t_d \) was noted in many human subjects when simultaneous sampling from radial or brachial artery was compared with the femoral artery.

With high outflow resistance of one branch of the model, similar differences appear when curves are recorded simultaneously from the proximal

![Diagram of blood flow](attachment:diagram.png)

**Fig. 6. Schematic representation of increased U/F in a side branch accomplished by increasing resistance \( R_p \).** Now the mixing length is an appreciable fraction of the total segment occupied by the aliquot of stroke volume. Below are seen the effects of two conditions of unequal flow.
and the distal end of the same branch (Figure 7). The proximal curve is similar to a record obtained from a branch with normal outflow resistance; the distal curve is similar to that from the constricted branch of Figure 6, so that the difference in curve parameters sampled from these two sites of the same “vasoconstricted” branch is essentially the same as the difference obtained from one normal and one constricted branch. This is more marked when the resistance in the sampled tube is further increased.

Finally, conditions of flow in a non-expansile system were simulated by causing such low outflow resistance that discontinuous (systolic) rather than continuous but pulsatile flow occurred. This solely systolic and presumably laminar flow did not cause distention of the rubber tubing and no appreciable elastic effect remained (Figure 8 left). Under these circumstances no distortion of contour was found. Likewise, when extreme, although unequal increase in resistance was applied to the two branches, there again was no distortion of proximal and distal curves obtained from one branch (Figure 8 right).

DISCUSSION

From the results obtained in the human studies, it is apparent that, in the absence of structural abnormality of the aorta, the FA curve invariably has values of $t_a$, $t_p$, and $t_d - t_a$ equal to or less than those of a simultaneous curve from another arterial site. Published curves of Fox and associates (2) indicate that the FA curve does not differ significantly from the curve obtained from the
abdominal aorta except for the expected brief and equal delay of all parameters. Comparison of curves obtained from the FA and FA following venous injection in normal subjects shows only a small, nearly constant alteration in contour (7). These observations support the conclusion that, when dealing with a normal arterial tree, the FA curve may be considered a close representative of its antecedent as it emerged from the left ventricle. The reason this site is unique among those commonly utilized may be the nearly pure forward flow patterns generally found with FA radiographic studies, except when mechanical obstruction is induced distal to the site studied. As a corollary, of all commonly used sites in man, the FA curve can be recorded with a minimum of delay and is not likely to imply a "Stewart" volume greater than the anatomical volume existing between aortic valve and sampling site. This conclusion is not warranted if gross aortic disease exists.

Curves from the BA may or may not differ from the FA curve in an apparently unpredictable manner. This correlates with variability of flow patterns seen in BA injection studies. Although the number of paired curves from the FA and RA is small, the latter curves show the most striking alterations and this is in keeping with the finding of slow clearance of radiopaque substance distal to the BA injection site even though severe alterations of flow patterns were not seen at that site.

The manner in which curves may be altered by arterial passage would seem to depend on local variation of flow and volume relations. The observed facts implicate two mechanisms, both of which are the consequence of local vasoconstrictive action: local regurgitation (return flow) because systolic uptake exceeds the runoff capacity of the segmental vascular bed, and a smaller systolic uptake over a prolonged time period because of a decrease in the compliance of the segment of arterial bed involved.

A suggested skewing mechanism

As stated, any explanation advanced for the mechanisms by which curves may be altered dur-

![Diagram](https://example.com/diagram.png)

**Fig. 8. (Left) The effects of pulsatile but nonexpansile flow.** There is no discernible effect due to laminar flow in the side branch. **(Right) Extremely high resistance in both branches; pulsatile, expansile flow.** Again only delay is seen in all portions of the curve from the distal site without skewing. This is similar to the curve from human subject, Figure 2.
The effects of this localized regurgitation can be examined further. Let us consider the course of events which follows the end of systole. (Assuming the pressure is nearly the same at all points in this small segment, one may consider diastole to begin at nearly the same time in all parts.) Consider first the fate of the blood immediately adjacent to the arterioles; this will flow continuously forward during diastole and in this it is similar to all the juxta-arteriolar blood. However, the blood and indicator, which at the end of systole are found at the entrance to this segment, reverse flow and enter another drainage area. The fate of blood at various intermediate points will generally fall between these extremes and theoretically there is a point in such a segment where the two opposite effects balance and no net flow occurs during diastole. These reasonable conclusions thus far have not caused an alteration of the time concentration curve as it traverses this aberrant segment since, at any given instant, the concentration is the same in both average and aberrant segments. A second abnormal condition is needed for dispersion to occur and to result in different concentrations in the two segments at a given time. This may be related to the manner in which systolic "penetration" occurs. In any segment a certain end-diastolic volume exists. The systolic uptake is smaller than the end-systolic volume, and to the extent that the latter exceeds the former, more than one stroke will be required until the indicator substances have completely traversed a segment. If diastolic flow is normally related to net systolic uptake, i.e., equal \((U/F = 1)\), then the average traversal time may be considered equal to the volume of the segment divided by the arteriolar runoff per second. It follows that with diminished runoff and constant volume, this time would increase inversely as the runoff decreased. Note that this will allow a delayed \(t_a\) as seen in human and model curves, but not necessarily an alteration of the contour. This situation is encountered in Table I, Subject 7, and in Figures 2 and 8. A further essential is the distribution of small aliquots of each stroke volume (systolic ejection) over an additional volume (and between one another). Since it has been stipulated that the stability of the curve as normally seen is due to a short longitudinal mixing distance and the relatively much greater length of homogeneous concentration, it is possible to increase the dispersion and alter the curve either by decreasing the length of homogeneous concentration, by increasing the length of longitudinal exchange, or by allowing longer time for longitudinal mixing. When small aliquots of aortic ejection enter a segment with increased ratio of \(U/F\) so that several successive short subsegments have different concentrations, and if conditions within the segment allow a significant degree of longitudinal mixing, we finally have all three conditions necessary for definite alteration of the input curve. The cir-
cumstances encountered in an “average” U/F segment are shown schematically in Figure 5. It will be noted that there are long distances of homogeneous concentration and short distances over which mixing can occur. This situation is contrasted with a high ratio U/F segment in which the distance between blood with two concentration levels may be of the same order as the distance of mixing (Figures 6 and 7).

Correlation of the theoretical mechanism outlined and the observed abnormalities follows. As successive small volumes of increasing concentration enter the segment of high U/F and move more slowly, as in Figures 6 and 7, a delayed t is to be expected. However, the mixing effect will cause an apparent “advance” of the appearance time $t_a$ since it is delayed less than $\bar{t}$; $\bar{t}$ is not affected by the mixing process which is bidirectional and of equal magnitude. Since $t_a$ is delayed less than $\bar{t}$, the first part of the curve is longer than the simultaneous curve recorded from the undisturbed segment. After peak concentration is reached, and decreasing concentration occurs with successive strokes, the mixing of aliquots of several strokes now slows the clearance, i.e., $t_d - t_p$ is longer in the segment with a high U/F. The human studies, Figure 1A and B, and model studies, Figures 6 and 7, are equivalent examples of this.

Of interest is the effect of mechanical obstruction on the contour of the dilution curve. Subject 8 (Table I), a patient with mild aortic coarctation, exhibited little functional evidence of obstruction (8) and showed the usual relations between FA and BA artery curves. Subject 9, with severe but incomplete obstruction, exhibited delay and skewing of the FA curve as compared to the BA curve, the reverse of the usual finding. This alteration of the FA curve is probably primarily caused by the increased U/F ratio distal to the obstruction rather than by the presence of collateral pathways of variable transit times. This is suggested from the evidence that the alteration of the FA curve is similar to that seen in BA when increased U/F is suspected. Beard and co-workers (1) have shown that the delay of the FA curve is corrected following repair of the coarcted segment.

The theoretical concepts presented above fit the observed differences in human studies and receive support from cinefluorographic studies which have demonstrated the transformation of a normal brachial artery flow pattern to a “regurgitant” and almost stagnant flow pattern by local vasoconstrictive reactions. Model studies clearly show that, if there is no disproportion of U/F allowed in the analog, the curve is nearly identical in all sites measured and the effects of laminar flow cannot be discerned. These methods of investigation also yielded results compatible with the theory that a curve may be altered by slow movement of a vascular column containing several different concentration levels where increased local mixing is possible. All of these are consequences of the increased U/F ratio of that segment.

Although it has been convenient to consider certain portions of the peripheral arterial tree as extensions of “sampling system dead space” (2, 9), it is obvious from Table I that the effects of this type of dead space are quite variable and a single curve could not be analyzed by the approaches which Sherman, Schlant, Kraus and Moore (6) have applied to catheter sampling systems. For this reason, it is suggested that in the consideration of possible alteration of dilution curves only the predictable, measurable invariant “dead space” be used in corrective manipulation.

**SUMMARY**

Of all commonly used arterial sampling sites, the femoral artery is most likely to yield a curve which most closely approaches the curve as it emerges from the left ventricle and this curve will be recorded with the least delay. Variable alteration of one or more curve parameters was frequently seen when simultaneous brachial artery or radial artery curves were compared with those from the femoral artery. The distortion encountered may assume proportions which would lead to serious inaccuracy in the estimation of appearance time, mean circulation time and disappearance slope.

Radiopaque injections into the femoral and brachial arteries of human subjects without arterial disease show extremely variable flow patterns in the brachial artery but not in the femoral artery. This is apparently due to local vasoconstriction.

A simple branched model characterized by pulsatile flow in an elastic system, with dimensions of capacity and stroke volume proportional to those of the human large arterial bed, could duplicate all variations of dilution curves seen in the human
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studies by means of altered resistance to flow in the two branches.

In the absence of pulsatile, elastic flow in the model, alteration of the curves was not seen, thus indicating that the parameters measured were insensitive to the effects of laminar flow and longitudinal mixing.

It is concluded that whenever possible the femoral artery in humans should be the most distal sampling site used when accurate reproduction of the contour of the curve and accurate estimation of the arterial volume included in the "Stewart" or "needle to needle" volume is required.

A high degree of coarctation of the aorta and presumably obstructive disease of the great vessels or aneurysmal dilatation of the thoracic or abdominal aorta render the femoral artery curve invalid for accurate applications of a dilution curve.

REFERENCES