Peripheral Vascular Volumes and Whole Body Hematocrit During Human Heart Lung Bypass

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SUMMARY
Indicator-dilution curves were obtained across the peripheral vascular bed in 15 patients soon after the beginning of heart lung bypass, and in eight of these persons they were repeated just prior to the conclusion of bypass. A bolus containing labelled red cells and albumin was injected into the arterial inflow line just proximal to the aorta. Serial blood samples were obtained at intervals of 1 second from the venous return line, just distal to the right atrium, and the radioactivity was measured. The interposed volume of blood in the pump oxygenator delayed recirculation, allowing extrapolation of the exponential downslope and calculation of flow rates and indicator distribution volumes by the Hamilton-Stewart equations.

The distribution volume of albumin (average, 56.3 ml/kg) was always greater than that of red cells (average, 44.8 ml/kg). The average ratio of whole body hematocrit to perfusate hematocrit was 0.873. The absence of significant differences between data obtained at the beginning and just prior to the end of bypass suggests that there were no alterations in venous tone or the volume relationships of large vessels to the microcirculation.

Additional Indexing Words:
Albumin transit time Peripheral circulation Red cell transit time
Blood flow Isotopes

VASCULAR VOLUME during cardiopulmonary bypass has been a confusing subject. Few quantitative hemodynamic studies have been performed during human heart lung bypass, and the canine data may not be applicable to man. Dogs usually undergo an anaphylactic-like reaction with splanchnic vascular congestion and dilatation and continued uptake of blood, when the extracorporeal circuit is primed with homologous blood.1 2 Knowledge of possible changes in vascular volumes during cardiopulmonary bypass and open intracardiac operations is important to proper treatment of the patient during and after operation.

The Hamilton-Stewart indicator-dilution technic can be used to measure rapidly the volume of the systemic circulation due to certain unique features of cardiopulmonary bypass. The interposed volume of blood in the pump oxygenator delays recirculation, and the exponential portion of the downslope of the first circulation can easily be identified (fig. 1). Using this principle, we measured vascular volume during bypass in dogs. The animals continued to gain weight during perfusion, but systemic vascular volume was fairly constant, indicating that the presumed fluid

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increase was in extravascular sites. A preliminary report of the application of this technic to man has also been published.

**Methods**

**Clinical Material**

This paper presents data from eight patients in whom indicator-dilution curves were obtained, with simultaneous injection of red cells and serum albumin at the beginning, and just prior to the conclusion of open heart lung bypass. Data from seven other patients, who had similar studies only at the beginning of bypass, are also included.

The general data concerning these 15 subjects are presented in table 1. The ages of the eight patients who had indicator-dilution curves made at the beginning and end of bypass, ranged from 8 to 61 years. Two had congenital abnormalities, and the other six had valvular rheumatic heart disease. The ages of the seven additional patients who had curves made only at the beginning of bypass ranged from 18 to 51 years.

**Operative Conditions**

Each patient was given 10 drops of Lugol's solution preoperatively. All the operations were performed via a median sternotomy, with a rotating disc oxygenator and a rotary arterial perfusion pump. The arterial pump was totally occlusive against a line pressure of 600 mm Hg and delivered a nonpulsatile flow. Line pressure during bypass seldom exceeded 150 mm Hg. The perfusion flow rate was estimated from the revolutions per minute of the pump, since these

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>HT (cm)</th>
<th>WT (kg)</th>
<th>BSA* (m²)</th>
<th>Diagnosis†</th>
<th>Operation‡</th>
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<td>C.J.</td>
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<td>MS, MI, AI</td>
<td>MV, AV</td>
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<td>CASD</td>
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<td>AV</td>
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<tr>
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<td>MC</td>
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<td>50</td>
<td>1.46</td>
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<tr>
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<td>MS</td>
<td>MC</td>
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<tr>
<td>C.F.</td>
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<td>51</td>
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<td>M.T.</td>
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<td>1.46</td>
<td>MS, MI</td>
<td>MV</td>
</tr>
<tr>
<td>A.D.</td>
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<td>165</td>
<td>51</td>
<td>1.55</td>
<td>AI</td>
<td>AV</td>
</tr>
</tbody>
</table>

* BSA = body surface area, m².
† Diagnosis: AI = aortic insufficiency; AS = aortic stenosis; ASD = atrial septal defect; MS = mitral stenosis; MI = mitral insufficiency; PS = pulmonic stenosis.
‡ Operation: AV = aortic valve replacement; MC = mitral commissurotomy; MV = mitral valve replacement; CASD = closure atrial septal defect; PC = pulmonary commissurotomy.
were linearly related to flow. The revolutions were
directly counted with a tachometer attached to
the pump head. After the perfusion, the flow rate
was accurately determined by timed pumping of
the blood at the same number of revolutions per
minute through the entire perfusion line into a
burette. The arterial perfusion line was intro-
duced in a retrograde fashion via an external iliac
artery in the first four patients and directly into
the ascending arch in the remaining 11. Venous
return was by gravity to the oxygenator, through
a single 38-F fenestrated cannula placed in the
right atrium. The pulmonary artery was encircled
with a Rommel tourniquet, which when constrict-
ed, diverted all blood to the venous return
cannula. The flow rate was 2.2 L/min/m² or
higher. The pump oxygenator was primed with
citrated blood, converted with heparin and
calcium gluconate, and diluted with buffered
Ringer's lactate. The hematocrit of the perfusate
ranged from 30.3 to 38.6. Moderate hypothermia,
28 to 30 C, was employed during each perfusion.
The oxygenating gas mixture was 97.5% Ω₂ and
2.5% CO₂, to which halothane was added.

Arterial blood pressure was obtained from a
radial artery, and central venous pressure, from
either the right atrium or the inferior cava. The
arterial blood was analyzed for pH and oxygen
and carbon dioxide tensions at the time of the
curves. The temperature of the blood in the
arterial and venous perfusion lines was constantly
monitored.

Method of Obtaining Curves

Red cells, drawn either from the patient or
from a cross-matched donor pack, were incubated
at 37 C for 1 hour with 200 μc of ⁵¹chromium, as
sodium chromate, and washed twice in normal
saline. Fifty microcuries of ¹²⁵I serum albumin
were added to the red cell suspension. The total
volume of the mixed isotopes was approximately
20 ml. In one of the patients (N.T.), only
¹²⁵albumin was injected.

Within a few minutes after beginning bypass,
as soon as it was determined that perfusion was
satisfactory, and prior to cooling, the inferior
caval or right atrial pressure was regulated at 10
mm Hg, by constricting the venous return
cannula. Then a bolus 4 to 6 ml of labelled red
cells and albumin was rapidly injected from a
calibrated syringe into the arterial inflow line.

Approximately 60 μc of chromium and 15 μc
of albumin were thus injected for each curve. At
the conclusion of bypass between one half and
two thirds of this activity was in the blood in the
pump oxygenator and was discarded. The
injection was just proximal to a fine meshed filter,
causing complete mixing of the isotopes with the
blood stream. Three to four milliliters of blood
was removed per second in a continual stream by

a small rotary pump from the venous return line.
The withdrawal site was about 10 cm distal to a
screw clamp on the venous line that regulated
venous pressure. This clamp created turbulence,
insuring complete mixing of the blood stream.
The withdrawn blood was pumped into separate
test tubes each second for 2 minutes. Aliquots of
2 ml were obtained from each tube, and
radioactivity from ¹²⁵I and ⁵¹Cr was measured
over a 5-min period in a Packard auto-gamma
spectrometer. Similar studies were made prior to
the conclusion of bypass in eight patients. Perfu-
sion rate and venous or right atrial pressure were
adjusted to be the same value as they were during
the sampling for the first curve. All of the patients
were rewarmed prior to obtaining the second
curve. The temperature of both the arterial and
venous return blood had reached 36 to 38 C, but
the rectal temperature usually was 34 to 36 C. Thus
the body thermal conditions were not

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**Figure 2**

Direct tracings made from the computer plots: (A)
Of the labelled albumin and red cell counts from
the first curve of patient A.S. The maximum value for
each isotope is plotted at the same distance along the
ordinate. (B) Of the logarithm of albumin and red cell
counts. The determination of the segments for ex-
trapolation of the downslopes was made by the
computer.
exactly similar to those of the initial curve but represented the conditions that usually obtain at the end of clinical perfusion.

After the operation was completed and the flow rate calibrated, the pump oxygenator and perfusion tubing were emptied of blood and filled with water. The arterial and venous lines were connected, and the perfusion rate and disc rotation speed were also set at the perfusion levels. The amount of water was adjusted to be approximately equal to the amount of blood that was in the extracorporeal circuit at the time the curves were obtained. Then a bolus of Evans T-1824 dye was injected into the arterial line, and the time of its visual reappearance at the injection site was measured, which represented the extracorporeal circulation time. The time from injection until the first appearance of indicator in the dilution curves, which gave the minimal transit time in the peripheral circulation, was added to the extracorporeal recirculation time to obtain the total recirculation time for the dilution curves. The volume of the extracorporeal tubing, included between the injection and sampling sites, was measured and subtracted from the calculated distribution volumes of both isotopes to obtain their respective distribution volumes within the peripheral vascular bed.

Tests performed showed that the maneuvers of handling the isotopes after collection from the venous return line did not cause any loss of isotope onto glassware or plastic test tubes. It was also proved that the degree of settling of red cells in the counting tubes did not affect the albumin or red cell counts. To quantitate the injectate, the same volume of the isotope mixture used in the study was injected into a volumetric flask and diluted to 1,000 ml, and five 2-ml aliquots were counted along with the other tubes, and averaged. This value was 1/500 of the total

**Table 2**

| Patient | $Q_0$ | pH | $Paco_2$ | $Pao_2$ | ABP | VBP | PVR | °C | $Het_{per}$ | Time
|---------|------|----|---------|--------|-----|-----|-----|----|-----------|------
| C.V.    | 3280 | 64.3 | 7.37    | 35.6   | 66.5 | 55  | 10.5 | 1084 | 37 | 38.7     | 4.5
|         | 3280 | 64.3 | 7.54    | 39.6   | 49.2 | 80  | 11   | 1681 | 37 | 37.6     | 2'51"
| C.T.    | 3400 | 60.7 | 7.38    | 32.7   | 62.0 | 50  | 10   | 940  | 37 | 34.5     | 6"
|         | 3400 | 60.7 | 7.54    | 37.7   | 45.5 | 48  | 10.5 | 881  | 37 | 34.5     | 2'26"
| R.P.    | 3320 | 67.7 | 7.38    | 34.0   | 85.1 | 45  | 10.5 | 830  | 36 | 35.0     | 9"
|         | 3320 | 67.7 | 7.39    | 36.5   | 72.5 | 62  | 9.5  | 1264 | 37 | 35.1     | 37"
| E.B.    | 2280 | 60.0 | 7.38    | 31.0   | 261  | 60  | 10   | 1753 | 37 | 34.0     | 19"
|         | 2280 | 60.0 | 7.43    | 34.5   | 246  | 53  | 10   | 1507 | 37 | 34.0     | 1'22"
| K.M.    | 3500 | 61.4 | 7.51    | 26.3   | 66.3 | 57  | 10   | 1073 | 36 | 38.6     | 10"
|         | 3500 | 61.4 | 7.54    | 28.4   | 58.5 | 40  | 11   | 662  | 36.5 | 33.3    | 53"
| A.S.    | 2080 | 94.5 | 7.21    | 32.9   | 193  | 55  | 9.5  | 1748 | 37 | 36.5     | 11"
|         | 2080 | 94.5 | 7.30    | 33.5   | 250  | 55  | 9.5  | 1748 | 37 | 37.4     | 43"
| N.T.    | 5000 | 67.6 | 7.34    | 38.6   | 71.4 | 36  | 10   | 416  | 37 | 34.0     | 13"
|         | 5000 | 67.6 | 7.47    | 38.8   | 401  | 70  | 10   | 959  | 37 | 37.3     | 1'39"
| A.SL.   | 4800 | 80.0 | 7.37    | 45.4   | 58.1 | 45  | 11   | 581  | 37 | 33.7     | 7"
|         | 4680 | 80.0 | 7.49    | 43.2   | 66.6 | 53  | 10   | 734  | 37.5 | 30.3    | 1'52"
| L.K.    | 2880 | 68.6 | 7.45    | 30.5   | 78.5 | 50  | 9.5  | 1124 | 36.5 | 35.6    | 10"
|         | 2880 | 68.6 | 7.36    | 40.5   | 72.5 | 50  | 12   | 803  | 37 | 36.5     | 25"
| M.M.    | 2800 | 56.0 | 7.50    | 25.3   | 46.5 | 35  | 10   | 552  | 36.5 | 36.4    | 9"
| E.N.    | 3620 | 63.5 | 7.50    | 25.3   | 46.5 | 35  | 10   | 552  | 36.5 | 36.4    | 9"
| C.F.    | 3360 | 70.0 | 7.44    | 25.9   | 41.5 | 40  | 11   | 690  | 37 | 39.4     | 13"
| J.S.    | 3120 | 61.2 | 7.38    | 27.0   | 48.0 | 60  | 10   | 1281 | 37 | 37.0     | 6"
| M.T.    | 4170 | 86.9 | 7.38    | 39.2   | 49.4 | 30  | 10   | 383  | 36.5 | 36.0    | 10"
| A.D.    | 3780 | 74.1 | 7.36    | 40.5   | 72.5 | 50  | 12   | 803  | 37 | 36.5     | 25"

* $Q_p$ = flow rate of pump (ml/min).
† $Q_p$ = flow rate of pump (ml/min/kg).
‡ Arterial gas tensions (mm Hg).
§ Mean arterial blood pressure (mm Hg).
** Mean venous blood pressure (mm Hg).
†† Peripheral vascular resistance (dyne cm-5).
‡‡ Arterial blood temperature.
§§ Hematocrit of perfusate.
*** Time from beginning of perfusion (min and sec).

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injected activity. With each series of the tubes counted, a sample of $^{51}$Cr was included in order to determine the percentage of counts in the $^{51}$Cr channel that appeared in the $^{125}$I channel. This varied from approximately 13 to 18%, depending upon window settings. (There is no overlap of $^{125}$I into the $^{51}$Cr channel.) The radioactive levels for chromium and albumin were corrected for background and transferred to punch cards, and all subsequent calculations were performed by a digital computer (IBM 7040/7044 via Quicktran terminal). The computer also plotted the curves for each isotope in two ways: simultaneous red cell and albumin curves (fig. 2A) and separate, semilogarithmic plots of each indicator (fig. 2B). The perfusion rates and mean indicator-transit times were determined from the red cell and serum albumin curves by conventional equations.\(^7\) The distribution volumes for cells and albumin were obtained by multiplying their respective mean transit times by the pump flow rate, which was precisely known and was obviously equal for both indicators. Correlation coefficients were obtained between various perfusion parameters and data from the indicator-dilution curves.

### Results

#### Perfusion Conditions

These data are given in table 2. The striking features are the tendencies for low vascular resistance and low arterial oxygen tension. During 16 of 23 curves, mean arterial blood pressure was 55 mm Hg or lower; in 12 of the 23 curves peripheral vascular resistance was less than 1,000 dyne sec cm\(^{-5}\); the lowest was 383 dyne sec cm\(^{-5}\). Arterial blood oxygen tension was less than 75 mm Hg during 15 of 21 curves. (Values were not obtained during two curves from one patient.)

#### Nature of the Curves

Figure 2 presents the total venous return curve from patient A.S. All the curves had this general configuration. There was a single peak for each indicator, that for albumin was always later than the red cell peak. The downslope usually had several exponential components. The terminal component was

### Table 3

**Flow Rate Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>$Q_p$ (ml/min)</th>
<th>$Q_{alb}$ (ml/min)</th>
<th>$Q_{alb}/Q_p$</th>
<th>$Q_c$ (ml/min)</th>
<th>$Q_c/Q_p$</th>
<th>$Q_{alb}/Q_c$</th>
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</table>

Average  1.043  0.966  1.059

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Abbreviations: $Q_p$ = pump flow rate; $Q_{alb}$ = albumin flow rate; $Q_c$ = cell flow rate (ml/min).
extrapolated to determine the total curve of first circulation.

**Flow Rates**

These are presented in table 3. In patient C.T., the two flow rates calculated from the red cell curves, \( Q_c \), are omitted because each was more than 50% greater than pump flow, suggesting a methodologic error. The albumin curve data from this patient and from N.T., whose study consisted only of albumin-dilution curves, were not used in calculating the mean values for flow rate derived from the albumin curves, \( Q_{alb} \), nor in the mean ratios of \( Q_{alb} \) to pump flow, \( Q_{alb}/Q_p \). Calculated flow rates, \( Q_{alb} \) and \( Q_c \), correlated reasonably well with the known pump flow rate, \( Q_p \) (\( r_{18} = 0.947 \) and \( r_{18} = 0.964 \), respectively; \( P < 0.001 \)). \( Q_{alb} \) was also well correlated with \( Q_c \) (\( r_{18} = 0.942; P < 0.001 \)), although \( Q_{alb} \) was greater then \( Q_c \) in 16 of 19 curves. Although neither mean \( Q_{alb} \) nor mean \( Q_c \) differs significantly from mean \( Q_p \), analysis of variance reveals that mean \( Q_{alb} \) is significantly higher than mean \( Q_c \) at the 5% level. Since regression analysis of flow rate on weight and body surface area, respectively, revealed the presence of significant intercepts, that is, a form corresponding to \( Q \) (ml/min) = \( Kx \) ± \( b \), where \( x \) is indicated either as \( m^2 \) or \( kg \), it is felt that the total flow rate affords a more direct basis for comparison. The linear regressions of \( Q_{alb} \) and \( Q_c \) on \( Q_p \) are summarized in table 4.

**Vascular Volume Data**

These data are presented in tables 5 and 6 for the 19 studies in which both indicators were used. \( V_{dalb} \) was well correlated with \( V_{d_e} \) (\( r_{17} = 0.97; P < 0.001 \)). The mean differences were found to be significantly different by variance analysis (\( P < 0.001 \)). Red cell volume (\( V_c \)) averaged 861.6 ± 204.8 ml, and plasma volume (\( V_p \)) averaged 1879.0 ± 494.9 ml. The whole body hematocrit (\( Hct_{WB} \)) was always smaller than the corresponding perfusate hematocrit (\( Hct_{PER} \)) with an average \( Hct_{WB}/Hct_{PER} \) ratio of 0.870 ± 0.873. There was no consistent change in \( V_c \), \( V_p \), or \( Hct_{WB}/Hct_{PER} \) between curves made at the beginning and those made just prior to the conclusion of bypass.

There was no correlation between \( Hct_{WB}/Hct_{PER} \) and either \( Q_p \) per kilogram or \( Hct_{PER} \).

**Interrelationships of Other Data**

The only significant change that occurred between the beginning and end of bypass was a mean rise in \( pH \) from 7.373 to 7.463. Scatter diagrams studying other relationships between several other variables failed to show significant correlations. Table 7 indicates the variables thus studied.

**Discussion**

**Evaluation of Methods**

Peripheral vascular resistance usually is reduced during bypass, especially at the beginning. Litwak et al.9 showed that hypotension can be induced by the slow exchange transfusion of perfusate from the pump oxygenator, without actual heart lung bypass. This suggests the presence of one or more vasodilating agents in the blood. There are several sources of such products during bypass. Red cell trauma releases adenosine triphosphate (ATP), a potent dilating agent.9

Table 4

| Linear Regressions of Albumin and Cell Flow Rates (\( Q_{alb} \) and \( Q_c \)) on Pump Flow Rate (\( Q_p \)) |
| --- | --- | --- |
| N = 19 | x = \( Q_p \) ml/min | x = \( Q_p \) ml/min |
| Mean x | 3264 | 3264 |
| Mean y | 3357 | 3170 |
| Regression coefficient (slope) | 1.09 | 1.09 |
| Intercept | -212 | -413 |

*Circulation, Volume XLI, April 1970*
## Table 5

**Vascular Volume and Hematocrit Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>$V_{d_{11b}}$ (ml)</th>
<th>$t_{11b}$ (sec)</th>
<th>$V_{p1}$ (ml)</th>
<th>$V_{d_{c}}$ (ml)</th>
<th>$t_{c}$ (sec)</th>
<th>$V_{c}$ (ml)</th>
<th>$t_{11b}/t_{c}$</th>
<th>Hct$_{PER}$ (%)</th>
<th>Hct$_{WB}$ (%)</th>
<th>Hct$<em>{WB}/$Hct$</em>{PER}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.V.</td>
<td>2549 ml</td>
<td>50.0 ml/kg</td>
<td>1660 ml</td>
<td>32.7 ml</td>
<td>44.3 ml</td>
<td>18.4 ml</td>
<td>1.13</td>
<td>38.7</td>
<td>36.0</td>
<td>0.929</td>
</tr>
<tr>
<td></td>
<td>3283 ml</td>
<td>64.4 ml/kg</td>
<td>2348 ml</td>
<td>46.0 ml</td>
<td>2403 ml</td>
<td>48.8 ml</td>
<td>1.32</td>
<td>37.6</td>
<td>29.9</td>
<td>0.796</td>
</tr>
<tr>
<td>C.T.</td>
<td>2488 ml</td>
<td>44.4 ml/kg</td>
<td>1754 ml</td>
<td>31.3 ml</td>
<td>2103 ml</td>
<td>37.6 ml</td>
<td>1.18</td>
<td>34.5</td>
<td>31.1</td>
<td>0.901</td>
</tr>
<tr>
<td></td>
<td>2609 ml</td>
<td>46.6 ml/kg</td>
<td>1833 ml</td>
<td>32.7 ml</td>
<td>2183 ml</td>
<td>39.0 ml</td>
<td>1.20</td>
<td>34.5</td>
<td>30.9</td>
<td>0.895</td>
</tr>
<tr>
<td>R.P.</td>
<td>2345 ml</td>
<td>47.8 ml/kg</td>
<td>1615 ml</td>
<td>33.0 ml</td>
<td>2040 ml</td>
<td>41.6 ml</td>
<td>1.15</td>
<td>35.0</td>
<td>32.1</td>
<td>0.916</td>
</tr>
<tr>
<td></td>
<td>2044 ml</td>
<td>41.7 ml/kg</td>
<td>1420 ml</td>
<td>29.0 ml</td>
<td>1649 ml</td>
<td>33.6 ml</td>
<td>1.24</td>
<td>35.1</td>
<td>30.7</td>
<td>0.876</td>
</tr>
<tr>
<td>E.B.</td>
<td>2787 ml</td>
<td>73.3 ml/kg</td>
<td>1922 ml</td>
<td>50.6 ml</td>
<td>2231 ml</td>
<td>58.7 ml</td>
<td>1.25</td>
<td>34.0</td>
<td>29.4</td>
<td>0.865</td>
</tr>
<tr>
<td></td>
<td>3183 ml</td>
<td>83.8 ml/kg</td>
<td>2183 ml</td>
<td>57.5 ml</td>
<td>2448 ml</td>
<td>64.4 ml</td>
<td>1.30</td>
<td>34.0</td>
<td>27.0</td>
<td>0.794</td>
</tr>
<tr>
<td>K.M.</td>
<td>3705 ml</td>
<td>65.0 ml/kg</td>
<td>2352 ml</td>
<td>41.3 ml</td>
<td>2920 ml</td>
<td>51.2 ml</td>
<td>1.27</td>
<td>38.6</td>
<td>33.3</td>
<td>0.863</td>
</tr>
<tr>
<td></td>
<td>3415 ml</td>
<td>59.9 ml/kg</td>
<td>2361 ml</td>
<td>41.4 ml</td>
<td>2862 ml</td>
<td>50.2 ml</td>
<td>1.19</td>
<td>33.3</td>
<td>29.6</td>
<td>0.890</td>
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<tr>
<td>A.S.</td>
<td>1224 ml</td>
<td>55.6 ml/kg</td>
<td>914 ml</td>
<td>41.5 ml</td>
<td>1036 ml</td>
<td>47.1 ml</td>
<td>1.18</td>
<td>36.5</td>
<td>32.7</td>
<td>0.908</td>
</tr>
<tr>
<td></td>
<td>1108 ml</td>
<td>50.4 ml/kg</td>
<td>826 ml</td>
<td>37.5 ml</td>
<td>998 ml</td>
<td>45.4 ml</td>
<td>1.11</td>
<td>37.4</td>
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<td>0.946</td>
</tr>
<tr>
<td>N.T.</td>
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<td>52.2 ml/kg</td>
<td>2657 ml</td>
<td>35.9 ml</td>
<td>2657 ml</td>
<td>35.9 ml</td>
<td>34.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2645 ml</td>
<td>35.7 ml/kg</td>
<td>1758 ml</td>
<td>23.8 ml</td>
<td>2645 ml</td>
<td>35.7 ml</td>
<td>37.3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>A.S.I.</td>
<td>2901 ml</td>
<td>49.6 ml/kg</td>
<td>2006 ml</td>
<td>34.3 ml</td>
<td>2598 ml</td>
<td>44.4 ml</td>
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<td>33.7</td>
<td>31.3</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>3114 ml</td>
<td>53.2 ml/kg</td>
<td>2257 ml</td>
<td>38.6 ml</td>
<td>2582 ml</td>
<td>44.1 ml</td>
<td>1.21</td>
<td>30.3</td>
<td>26.6</td>
<td>0.878</td>
</tr>
<tr>
<td>L.K.</td>
<td>2958 ml</td>
<td>70.4 ml/kg</td>
<td>1982 ml</td>
<td>47.2 ml</td>
<td>2180 ml</td>
<td>51.9 ml</td>
<td>1.36</td>
<td>35.6</td>
<td>29.2</td>
<td>0.821</td>
</tr>
<tr>
<td></td>
<td>3308 ml</td>
<td>66.2 ml/kg</td>
<td>2132 ml</td>
<td>42.7 ml</td>
<td>2331 ml</td>
<td>46.6 ml</td>
<td>1.42</td>
<td>38.5</td>
<td>25.6</td>
<td>0.665</td>
</tr>
<tr>
<td>M.M.</td>
<td>2505 ml</td>
<td>43.9 ml/kg</td>
<td>1688 ml</td>
<td>29.6 ml</td>
<td>2183 ml</td>
<td>38.3 ml</td>
<td>1.15</td>
<td>36.4</td>
<td>33.5</td>
<td>0.919</td>
</tr>
<tr>
<td>I.N.</td>
<td>1926 ml</td>
<td>40.1 ml/kg</td>
<td>1383 ml</td>
<td>28.8 ml</td>
<td>1647 ml</td>
<td>34.3 ml</td>
<td>1.17</td>
<td>39.4</td>
<td>36.1</td>
<td>0.915</td>
</tr>
<tr>
<td>C.F.</td>
<td>2847 ml</td>
<td>55.8 ml/kg</td>
<td>1895 ml</td>
<td>37.2 ml</td>
<td>2330 ml</td>
<td>45.7 ml</td>
<td>1.22</td>
<td>37.0</td>
<td>32.7</td>
<td>0.884</td>
</tr>
<tr>
<td>U.S.</td>
<td>4111 ml</td>
<td>85.6 ml/kg</td>
<td>2737 ml</td>
<td>57.0 ml</td>
<td>3141 ml</td>
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<td>36.0</td>
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<td>0.841</td>
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<tr>
<td>M.T.</td>
<td>4025 ml</td>
<td>59.3 ml/kg</td>
<td>2026 ml</td>
<td>39.7 ml</td>
<td>2585 ml</td>
<td>50.7 ml</td>
<td>1.17</td>
<td>36.5</td>
<td>32.6</td>
<td>0.906</td>
</tr>
</tbody>
</table>

Abbreviations: $V_{d_{11b}}$ = distribution volume of albumin; $t_{11b}$ = mean transit time albumin; $V_{p1}$ = plasma volume; $V_{d_{c}}$ = distribution of red cells; $t_{c}$ = mean transit time red cells; $V_{c}$ = red cell volume; Hct$_{PER}$ = hematocrit of perfusate; Hct$_{WB}$ = whole body hematocrit.
Table 6

Mean Vascular Volumes and Hematocrit Values

<table>
<thead>
<tr>
<th></th>
<th>N = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Vd Alb (±sd)</td>
<td>2735 ± 718 ml</td>
</tr>
<tr>
<td></td>
<td>1187 ± 375 ml/m²</td>
</tr>
<tr>
<td></td>
<td>57.5 ± 12.7 ml/kg</td>
</tr>
<tr>
<td>Mean Vd c (±sd)</td>
<td>2228 ± 530 ml</td>
</tr>
<tr>
<td></td>
<td>1522 ± 253 ml/m²</td>
</tr>
<tr>
<td></td>
<td>46.8 ± 8.4 ml/kg</td>
</tr>
<tr>
<td>Mean t Alb (±sd)</td>
<td>54.54 ± 1458 sec</td>
</tr>
<tr>
<td>Mean t c (±sd)</td>
<td>44.41 ± 9.36 sec</td>
</tr>
</tbody>
</table>

Kinins may be released from plasma upon contact with the extracorporeal surfaces. Protein denaturation at the blood gas interface probably is not the cause, because we have used a membrane oxygenator for the past 6 months and the same degree of hypotension has occurred.

In other studies we have determined that during human bypass systemic vascular resistance is not related to the site of arterial inflow. With constant flow rate, arterial blood pressure is the same when perfusion is alternately made into the ascending aortic arch or retrograde into an external iliac artery. Furthermore, we have also found during clinical perfusion, that mean arterial pressure remains constant when pulsatile and nonpulsatile flow are alternately employed in the same subject.

Inability of the oxygenator to saturate the blood completely under the conditions of perfusion caused the frequent low arterial oxygen tensions. The oxyhemoglobin saturations associated with these low P_{O2} values were still 79% or greater, and with the flow rates employed, total oxygen delivery was adequate, and no adverse effects would be expected. There was no correlation between arterial oxygen tension and peripheral vascular resistance.

These curves are unique for two reasons. First, this experimental preparation provides the only way of obtaining curves across the entire peripheral circulation, because recirculation is delayed, allowing the downslope to be accurately plotted. Second, the true flow rate was known precisely because it was provided by the pump, which was accurately calibrated. Thus, differences in flow rates between those determined by the equation for calculating flow rate and the pump rates can be evaluated with respect to behavior of the indicators in the peripheral vasculature.

The intercept of the regression of flow rates determined from the albumin curves on pump flow was −212 ml/min and that for red cell flow −413 ml/min. This could be due to an undetected methodologic error in calculation of flow from the indicator-dilution curves.

The calculations assumed two conditions that were not totally true: first, that all of the indicator particles completed their initial transit early enough to be represented in the curve, and second, that no indicator was lost from the vascular bed in a single transit.

When labelled red cells or serum albumin are injected into an intact subject, total equilibration takes about 5 min, but takes longer in states of low cardiac output. This means that a small percentage of red cells and albumin molecules distribute themselves slowly into some regions. In the present study these slow regions would be expected to

Table 7

Summary of the Variables That Were Tested for Significant Correlation

<table>
<thead>
<tr>
<th></th>
<th>pHart</th>
<th>Mean BPart</th>
<th>Pco2art</th>
<th>P02art</th>
<th>PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qo (ml/kg)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>pHart</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Mean BPart</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vd c</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Vd Alb</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PVR</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

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receive some of the labelled cells and albumin during the initial transit, and these indicators would then return to the right atrium later than the rest of the labelled cells and albumin molecules and would not contribute to the curve.

Albumin is known to leave the vascular bed and enter lymph.\textsuperscript{14} Even though this is a slow process, some labelled albumin must leave in the initial transit and cannot be represented in the dilution curve obtained at the venous return site.

Each of these two mechanisms, slow transit time and loss of indicator, would cause a decrease in the recovered radioactivity counts and decreased curve area. The area of curve is the denominator in the equation for calculating flow rate, and thus a decreased area would increase the calculated flow value. Therefore, slowly circulating red cells would result in a calculated flow somewhat greater than the pump flow. For albumin, both the slow transit times plus leakage of albumin would combine to give flows higher than pump flow. Consequently, if there was no methodologic error, the calculated flows from both the albumin and red cell curves should always be equal to, or greater, but never less than pump flow.

\( Q_\text{e} \) averaged 94 ml/min less than pump flow, while \( Q_{\text{alb}} \) averaged 93 ml/min more than \( Q_\text{e} \). Neither of these differences was statistically significant, but the difference between \( Q_{\text{alb}} \) and \( Q_\text{e} \), averaging 187 ml/min, was significant at the 5\% level. This suggests that the loss of red cells during the first circulation was negligible and that all of the injected red cells returned to the right atrium early enough to be included in the dilution curve. By contrast, about 6\% of the injected albumin molecules did not contribute to the curve of first circulation, because of long transit times or escape from the vascular space.

If albumin molecules were lost from the circulation at the same rate in all portions of the vascular space, each 1-sec sample would contain a proportionately reduced number of labelled molecules, and the shape of the curve and the mean transit time would not be affected. If, on the other hand, the loss of albumin were greatest from portions of the vascular bed with long transit times, then the mean transit time would be underestimated.

We have obtained several dilution curves from the inferior vena cava, which suggest that the mean transit time across the splanchnic circulation is longer than that across the other vascular beds. This would be expected because of the passage through two capillary beds, the hepatic sinusoids, and the capillaries of the other splanchnic viscera. One would expect the greatest loss of albumin in this circulation because both of these beds are more permeable to albumin than is the general circulation.\textsuperscript{15} Thus, it is likely that the observed difference between \( t_{\text{alb}} \) and \( t_\text{e} \) is actually less than the real difference. We have not obtained sufficient data to compare the loss of albumin indicator from curves drawn separately from the superior and inferior venae cavae.

**Large Vessel Versus Whole Body Hematocrit**

The simultaneous red cell and albumin curves in this study are believed to be the first obtained in any species across the entire peripheral vascular bed. The average \( \text{Hct}_{\text{WB}}/\text{Hct}_{\text{FER}} \) was 0.873, similar to the values reported for the entire human vascular bed, employing the conventional methods for albumin and cells.\textsuperscript{16} This near identity may be coincidental. In intact subjects total body hematocrit is determined from the dilution of red cells and albumin after 15 to 20 min. During this interval red cells and albumin almost certainly equilibrate with regions of the vascular bed that are not permeated completely during a single transit.

Indicator-dilution curves similar to those in this study have been obtained across the intact human cerebral and pulmonary circulation. Larsen and Lassen\textsuperscript{17} found the cerebral hematocrit to be 92\% of \( \text{Hct}_{\text{LV}} \) in subjects in whom \( \text{Hct}_{\text{WB}}/\text{Hct}_{\text{LV}} \) averaged 0.89. An average ratio of pulmonary hematocrit to \( \text{Hct}_{\text{LV}} \) of 0.92 was reported by Rapaport et al.\textsuperscript{18}
The plasma volume measured by albumin molecules may not be entirely contained within the endothelial vascular boundaries. Axial streaming and plasma skimming probably do not occur in vessels above 0.3-mm diameter. Assuming a mean hematocrit value of small vessels that is half that of large vessels, Lawson estimated that the volume of blood in vessels less than 0.3-mm diameter can only account for 13% of the excess plasma volume. Since capillaries are known to be permeable to large molecules, the equilibrium distribution volume of albumin may include extra endothelial, pericapillary spaces. The same considerations probably apply to a single transit. It is possible, or even likely, that some of the albumin distribution volume in this study was outside the endothelial boundaries. Since 94% of the injected albumin was recovered, if an extra-endothelial space was perfused by albumin, there was rapid equilibration.

**Applicability of These Data to Other Methods of Perfusion**

Several aspects of heart lung bypass may be variably managed during a successful perfusion: flow rate, arterial pulse contour, perfusate hematocrit, arterial oxygen tension, and central venous pressure. Consequently, each surgical group conducts perfusion differently, and these data strictly apply only to the perfusion conditions of this study. However, consideration of the above variables suggests that our findings are also probably applicable to the perfusions carried out somewhat differently.

Most surgical groups perfuse at 2.2 L/min/m² or higher, thus providing normothermic oxygen requirements. Kinter and Pappenheimer found that the ratio of renal hematocrit to perfusate hematocrit decreased with increasing flow rate. Within the variations of perfusion rate per kilogram of body weight in this study there was no correlation between flow rate and ratio of HctWB to HctPER.

There are considerable data concerning the hemodynamics of pulsatile flow, but very few on the physiologic effects of pulsatile versus nonpulsatile flow. Recently it has been shown that organ function is satisfactorily preserved for longer periods when kidneys, segments of intestine, and the liver are perfused with pulsatile rather than with nonpulsatile flow. Therefore, pulsatile perfusion should also be superior for clinical heart lung bypass and probably will be adopted. Since pulsatile flow is transmitted to the microcirculation, ratio of HctWB to HctPER may be different under the two perfusion conditions.

Many surgical groups employ greater hemodilution than that used in this study. There was no correlation between any of the parameters and HctPER, the latter ranging from 30.3 to 39.4. Greater hemodilution may have produced differences in the distribution of red cells and plasma in the microcirculation. Pappenheimer and Kinter and Chinard et al. showed that the ratio of total renal hematocrit to perfusate hematocrit decreased as the latter was reduced.

All the commercially available oxygenators provide adequate arterial oxygen tensions when used properly. A carefully controlled experimental study might show effects of PaO₂ on some of the parameters measured in this study. However no correlation was found with a PaO₂ over a range from 45 to 401 mm Hg.

Venous pressure generally is not regulated during clinical heart lung bypass but is allowed to fall to whatever equilibrium level is reached using gravity venous return to the oxygenator. Venous pressure may become negative but usually is about 5 mm Hg. Thus, the constant level of 10 mm Hg in this study is higher than usual, and Vd per kg consequently must have been greater than in most perfusions. Little is known about the effects of venous pressure on the peripheral vascular bed during heart lung bypass. Read et al. reported that changes in venous pressure did not alter arteriolar tone in perfused dogs. Changes in venous pressure may influence perfusion of the microcirculation at constant flow rate and thus alter HctWB/HctPER.
Conclusions Regarding the Human Vascular Response to Heart Lung Bypass

These studies were not designed to evaluate the effects of alterations of perfusion parameters upon peripheral vascular volumes. We attempted to maintain constant perfusion conditions, so that the variations that did occur were random and usually small. Furthermore, there was wide variation among the patients with respect to the type and severity of their heart disease. Precisely controlled animal studies may demonstrate an effect of, for example, \( P_{\text{aO}_2} \) on \( V_d \), or on \( \text{Hct}_{WB}/\text{Hct}_{PER} \), whereas no correlations were found between any parameters of perfusion in this study.

The peripheral vascular volume relationships were not systematically different at the end of bypass compared to the beginning; this indicates that net vascular pooling does not occur during prolonged human heart lung bypass. Furthermore, there probably was not a major redistribution of blood volume between large vessels in different organs because the overall shape of the first and second curves was nearly the same. The similarity of the first and second \( \text{Hct}_{WB}/\text{Hct}_{PER} \) values suggests that the perfusion relationship of large vessels and the microcirculation were also unchanged.

While these data demonstrate that the peripheral vasculature is geometrically similar shortly after the beginning of bypass and just prior to its conclusion, they do not allow any additional conclusions to be made concerning the vasculature at other times during surgery. Measurements were not made of total and central blood volume prior to bypass, allowing calculation of systemic blood volume. Therefore, the relationship of systemic volume during bypass to the preoperative value is not known. It would not be surprising if the systemic vascular bed characteristics changed within seconds or a few minutes after the onset of bypass, before our first curves were obtained. Similarly, the vascular bed probably changes between the conclusion of bypass and the termination of anesthesia, and then during the postoperative recovery period.

Acknowledgment

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References

Peripheral Vascular Volumes and Whole Body Hematocrit During Human Heart Lung Bypass

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