Pulmonary Extraction of 5-Hydroxytryptamine and Norepinephrine before and after Cardiopulmonary Bypass in Man

By C. N. Gillis, N. M. Greene, L. H. Cronau, and G. L. Hammond

ABSTRACT

Pulmonary extraction of $^{14}$C-5-hydroxytryptamine and $^{3}$H-norepinephrine was estimated in patients undergoing aortocoronary saphenous vein grafting. Identical mixtures of both amines were administered intravenously before cardiopulmonary bypass and again just after bypass. Immediately after each injection, 6 ml of blood was withdrawn into tubing, at a constant rate, simultaneously from both the pulmonary artery and the left atrium. Each set of tubing was then divided into six segments, and the $^{3}$H and $^{14}$C content of each segment was measured. In this manner, total isotope collected and blood isotope concentration as a function of time at the two sampling sites were compared directly. Before bypass in every patient studied, less 5-hydroxytryptamine and norepinephrine were withdrawn on the left than on the right of the lungs, implying pulmonary extraction of both amines. In nine patients, the mean percent extraction was 65 ± 4% for 5-hydroxytryptamine and 23 ± 5% for norepinephrine ($P < 0.005$). After bypass, the percent extraction of both norepinephrine and 5-hydroxytryptamine was increased in all but one patient; values for norepinephrine were increased to a relatively greater extent. These data represent a direct demonstration of 5-hydroxytryptamine and norepinephrine extraction by human lungs and also suggest that total cardiopulmonary bypass may alter the process.

KEY WORDS  lung  pulmonary vascular space  amine extraction

Both 5-hydroxytryptamine (5-HT) and norepinephrine (NE) are removed, to varying degrees, from the pulmonary vascular space of dog (1–4), cat (5), rat (6, 7), guinea pig (8), and rabbit (9). Pulmonary venous and, thus, systemic arterial blood concentrations of these amines are significantly decreased by passage through the lung. The mechanisms and possible physiological significance of the process are unknown, though it has been suggested (10) that pulmonary clearance prevents vasoactive substances (including both NE and 5-HT) which are present in venous blood and which have essentially local actions from reaching the arterial circulation in effective concentrations.

That pulmonary inactivation of 5-HT might also occur in man receives indirect support from the fact that right-sided heart lesions predominate in patients with intestinal carcinoid tumors (11). Sandler (12) has proposed that certain symptoms of bronchial carcinoid tumors are due to bypassing of normal hepatic 5-HT inactivation mechanisms. However, if lung rather than liver is the major site of 5-HT inactivation (10), then these symptoms may likewise reflect inefficiency of pulmonary mechanisms for removal of 5-HT. Derangement of pulmonary extraction of 5-HT also may be related to the occurrence of postoperative venous thrombosis (8). Both hypotheses depend on the direct demonstration in man that 5-HT is removed from the pulmonary vascular space.
The present study was designed to evaluate pulmonary extraction of 5-HT and NE in man and to determine the effect of cardiopulmonary bypass on the extraction process.

Methods

Nine patients, who were undergoing coronary revascularization by aortocoronary saphenous vein bypass grafting, were studied. Each had radiologic evidence of severe coronary arterial disease. None had overt pulmonary disease. Table 1 lists relevant clinical data for each patient.

Patients were anesthetized with morphine and nitrous oxide; curare was used as a muscle relaxant. Induction doses of morphine ranged from 1.0 mg/kg body weight to 1.5 mg/kg; total doses administered during surgery ranged from 2 mg/kg to 3 mg/kg (13). Patients were ventilated with 50-60% nitrous oxide in oxygen before cardiopulmonary bypass and with 100% oxygen after bypass. Cardiopulmonary bypass was accomplished using a Bentley bubble oxygenator through which 100% oxygen was passed.

About 3-5 minutes after heparinization of the patient prior to cardiopulmonary bypass and again 5-10 minutes after bypass, needles connected to plastic tubes were placed in the pulmonary artery and the left atrium. The distal ends of each set of tubes were in turn attached to 20-ml syringes in a constant-rate withdrawal pump. After placement of sampling needles, 9-10 ml of a solution containing 14C-5-HT and 3H-NE was administered by rapid intravenous injection (in approximately 3 seconds) via a peripheral venous catheter, which was then flushed with blood under pressure.

Immediately after completion of isotope injection, withdrawal of blood from the pulmonary artery and the left atrium was started at a rate of 19.4 ml/min and continued for 30-35 seconds. Clamps were then applied to the tubing distal to the needles and proximal to the syringes. Each tube was divided into six segments between plastic clamps. After all clamps were in place, the tubing was transported to the laboratory, where, approximately 20 minutes after withdrawal, each segment was cut off in sequence beginning with the one nearest the patient (segment 6) and ending with the most distal segment (segment 1, containing blood withdrawn from the patient first). Segments were numbered and connected to a burette containing 0.4N perchloric acid, 3.0 ml of which was used to flush the blood into a preweighed centrifuge tube which was shaken thoroughly and placed in ice for approximately 20 minutes. Thereafter each centrifuge tube was weighed again, the weight of blood in each segment was calculated from this direct measurement. Precipitated proteins were sedimented by centrifugation at 10,000 g for 15 minutes. The volume of supernatant fractions was recorded, and the 14C and 3H content of each was determined in duplicate 0.2-ml aliquots with a Packard model 3320 liquid scintillation spectrometer.

Recovery of 3H-NE or 14C-5-HT added to blood in vitro and carried through one perchloric acid extraction was 78-90%. In ten separate determinations a second extraction of the precipitated protein with 2.0 ml of 0.4N perchloric acid

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**TABLE 1**

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Age</th>
<th>Wt (kg)</th>
<th>LVEDP (mm Hg)</th>
<th>Total bypass time (minutes)†</th>
<th>Surface area (m²)</th>
<th>Mean flow (ml/min)</th>
<th>Perfusion (ml/min/m²)</th>
<th>Hypothermia (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.W.</td>
<td>60</td>
<td>83</td>
<td>6</td>
<td>109 (22)</td>
<td>2.07</td>
<td>3210</td>
<td>1550</td>
<td>40</td>
</tr>
<tr>
<td>E.R.</td>
<td>58</td>
<td>66</td>
<td>3</td>
<td>95 (13)</td>
<td>1.80</td>
<td>2265</td>
<td>1470</td>
<td>20</td>
</tr>
<tr>
<td>A.P.</td>
<td>53</td>
<td>75</td>
<td>4</td>
<td>89 (7)</td>
<td>1.90</td>
<td>3000</td>
<td>1580</td>
<td>33</td>
</tr>
<tr>
<td>W.M.</td>
<td>64</td>
<td>75</td>
<td>10</td>
<td>88 (16)</td>
<td>1.85</td>
<td>3050</td>
<td>1650</td>
<td>37</td>
</tr>
<tr>
<td>R.K.H.</td>
<td>48</td>
<td>77</td>
<td>13</td>
<td>100 (14)</td>
<td>1.89</td>
<td>3300</td>
<td>1750</td>
<td>28</td>
</tr>
<tr>
<td>J.P.</td>
<td>64</td>
<td>78</td>
<td>6</td>
<td>170 (16)</td>
<td>1.79</td>
<td>2475</td>
<td>1580</td>
<td>42</td>
</tr>
<tr>
<td>L.J.</td>
<td>45</td>
<td>61</td>
<td>13</td>
<td>100 (17)</td>
<td>1.75</td>
<td>3040</td>
<td>1740</td>
<td>30</td>
</tr>
<tr>
<td>J.O.K.</td>
<td>43</td>
<td>69</td>
<td>22</td>
<td>168 (9)</td>
<td>1.81</td>
<td>3700</td>
<td>2020</td>
<td>52</td>
</tr>
<tr>
<td>M.A.</td>
<td>52</td>
<td>67</td>
<td>8</td>
<td>125 (39)</td>
<td>1.80</td>
<td>3850</td>
<td>2140</td>
<td>74</td>
</tr>
<tr>
<td>H.H.</td>
<td>61</td>
<td>63</td>
<td>18</td>
<td>69 (5)</td>
<td>1.75</td>
<td>4600</td>
<td>2640</td>
<td>33</td>
</tr>
<tr>
<td>M.L.</td>
<td>46</td>
<td>57</td>
<td>NA</td>
<td>98 (19)</td>
<td>1.59</td>
<td>4600</td>
<td>2000</td>
<td>60</td>
</tr>
</tbody>
</table>

LVEDP = left ventricular end-diastolic pressure; NA = data not available.

*All patients except M.L. were males; all had clinical diagnosis of occlusive coronary arterial disease.

†Numbers in parentheses indicate minutes on partial bypass.

<table>
<thead>
<tr>
<th>Hypothermia (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

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yielded only an additional $13.7 \pm 1.1\%$ (se) of total radioactivity added. Accordingly, the second extraction was not carried out routinely.

Total isotope collected at both sampling sites was calculated by adding the total amount of each isotope in the six segments obtained from the pulmonary artery and the left atrium, respectively. In addition, the concentrations of isotopes (counts/min g$^{-1}$ blood) in each segment were calculated and expressed graphically. The difference between total isotope entering and leaving the lung yields a direct measure of pulmonary extraction of each amine (see below).

**PREPARATION OF ISOTOPE FOR INJECTION**

$^3$H-NE (specific activity 5 c/mM) and $^{14}$C-5-HT (as the creatinine sulfate, specific activity 55 mc/mM) were obtained from the New England Nuclear Corporation and the Nuclear Chicago Corporation, respectively. $^3$H-NE was initially diluted with unlabeled NE to a specific activity of 1.27 c/mM. No longer than 24 hours before use, 1 ml of this solution (13.4 $\mu$g NE base, 100 $\mu$c) was purified by passage over alumina (14). After elution from alumina in 0.2n HCl, NE was mixed with 50 $\mu$c (15.3 $\mu$c) of 5-HT base and dissolved in 0.2n HCl; the mixture was then brought to a total volume of 8 ml with 0.2n HCl. Two 4-ml portions of the isotope mixture were passed through 0.22$\mu$ Millipore bacterial filters into multidose vials. Two 1-ml portions of sodium lactate buffer (2.5 mEq/ml) were also sterilized by passage through Millipore filters into sterile vials. The isotope mixture and the lactate buffer were held at 4°C until use. This method of preparation ensured that the relative concentrations of $^{14}$C and $^3$H administered to each patient before and after cardiopulmonary bypass was identical. Just prior to injection, one vial containing isotope mixture and one containing lactate buffer were mixed with 5 ml of sterile 0.9% sodium chloride, yielding a total volume of 9-10 ml (pH approximately 4.5) for injection.

In two experiments, 1-2 ml of perchloric acid supernatant fluid was used to determine specifically $^3$H-NE and $^{14}$C-5-HT. $^3$H-NE was measured in HCl eluates of alumina columns (14), and $^{14}$C-5-HT was extracted into isomyl alcohol at pH 10 by the technique of Eccleston et al. (15). The significance of data was evaluated by the t-test for paired samples (16).

**Results**

Typical isotope concentration profiles obtained in two patients are presented in Figure 1. Pulmonary arterial concentration profiles of $^{14}$C and $^3$H before bypass were qualitatively similar; isotope concentration decreased rapidly in both patients. In neither patient was a concentration peak seen. In fact, a well-defined pulmonary arterial peak of isotope concentration was observed only once in nine patients prior to bypass. In contrast, there was a definite peak of isotope concentration in pulmonary arterial blood after bypass. As can be seen in Figure 1, before bypass the decline in left atrial isotope concentration was less rapid than that in the pulmonary artery. However, after bypass, left atrial samples showed increasing isotope concentrations, which frequently reached a maximum at, or just before, the last sampling interval (Fig. 1).

Isotope, whose concentration is reflected in the last sample removed from the pulmonary artery, could not completely have crossed the pulmonary vascular bed before the end of withdrawal, which was complete in 30-35 seconds; also the first left atrial sample reflects isotope that was not sampled at the pulmonary artery. Accordingly, the effect of neglecting the last pulmonary arterial and the first atrial samples in determining total isotope extraction was evaluated. Table 2 lists percent extraction of 5-HT and NE in each of nine patients before cardiopulmonary bypass and shows that in all patients extraction of 5-HT was significantly greater ($P<0.005$) than that of NE, whether five or six samples were used in calculating total isotope withdrawn at each site. However omitting the last pulmonary arterial and the first left atrial samples significantly ($P<0.01$) increased the calculated percent extraction of $^3$H-NE and $^{14}$C-5-HT. Table 2 also shows percent extraction of both amines in each of seven patients immediately after cardiopulmonary bypass. There was no significant difference when percent extractions of 5-HT or NE after bypass calculated using five and six samples were used. When five sampling intervals were used in the calculation, extraction of both NE and 5-HT was significantly increased ($P<0.01$) after bypass.

**PERCENT OF TOTAL $^3$H AND $^{14}$C ASSOCIATED SPECIFICALLY WITH NE AND 5-HT**

In two experiments $^3$H-NE and $^{14}$C-5-HT of each left atrial and pulmonary arterial sample

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Isotope concentrations in blood withdrawn continuously for approximately 30 seconds from the pulmonary artery (P.A.) and the left atrium (L.A.) both before and after cardiopulmonary bypass in two representative patients. Immediately after injection of a mixture of \textsuperscript{1}H-norepinephrine and \textsuperscript{14}C-5-hydroxytryptamine, withdrawal of blood was begun. In each isotope concentration profile illustrated, the first point on the left represents isotope concentration in the first blood sample withdrawn; the last point on the right reflects isotope concentration in the sixth and last sample withdrawn.

### TABLE 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>\textsuperscript{14}C-5-hydroxytryptamine Before bypass (%)</th>
<th>\textsuperscript{14}C-5-hydroxytryptamine After bypass (%)</th>
<th>\textsuperscript{1}H-norepinephrine Before bypass (%)</th>
<th>\textsuperscript{1}H-norepinephrine After bypass (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.W.*</td>
<td>76.9 (76.0)</td>
<td>89.8 (89.0)</td>
<td>7.0 (3.0)</td>
<td>82.6 (82.1)</td>
</tr>
<tr>
<td>E.R.</td>
<td>67.4 (68.8)</td>
<td>73.1 (74.5)</td>
<td>47.9 (38.8)</td>
<td>21.6 (19.6)</td>
</tr>
<tr>
<td>A.P.</td>
<td>54.7 (49.6)</td>
<td>14.8 (8.6)</td>
<td>22.5 (21.5)</td>
<td>71.8 (76.5)</td>
</tr>
<tr>
<td>W.M.*</td>
<td>80.0 (78.0)</td>
<td>34.2 (24.4)</td>
<td>23.3 (14.1)</td>
<td>90.2 (92.6)</td>
</tr>
<tr>
<td>R.K.H.</td>
<td>53.0 (47.3)</td>
<td>27.6 (16.1)</td>
<td>22.5 (14.1)</td>
<td>19.1 (19.0)</td>
</tr>
<tr>
<td>J.P.</td>
<td>30.4 (45.1)</td>
<td>79.1 (77.6)</td>
<td>1.0 (2.2)</td>
<td>29.4 (21.5)</td>
</tr>
<tr>
<td>M.A.</td>
<td>76.9 (73.3)</td>
<td>32.2 (21.5)</td>
<td>1.0 (2.2)</td>
<td>29.4 (21.5)</td>
</tr>
<tr>
<td>H.H.</td>
<td>62.3 (57.6)</td>
<td>31.6 (17.8)</td>
<td>23.3 (16.7)</td>
<td>49.5 (47.0)</td>
</tr>
<tr>
<td>M.L.</td>
<td>64.0 (58.2)</td>
<td>35.4 (31.6)</td>
<td>23.3 (16.7)</td>
<td>49.5 (47.0)</td>
</tr>
<tr>
<td>MEAN</td>
<td>65.9 (61.6)</td>
<td>80.7 (80.6)</td>
<td>23.3 (16.7)</td>
<td>49.5 (47.0)</td>
</tr>
<tr>
<td>SE</td>
<td>± 3.7 (± 4.3)</td>
<td>± 2.8 (± 3.3)</td>
<td>± 4.8 (± 3.8)</td>
<td>± 11.6 (± 13.1)</td>
</tr>
</tbody>
</table>

Values are percent extraction calculated according to formula \(\frac{(\text{P.A.} - \text{L.A.})}{\text{P.A.}} \times 100\), where P.A. = sum of total isotope in samples 1-5 withdrawn from pulmonary artery and L.A. = sum of total isotope in samples 2-6 withdrawn from left atrium. Percent extraction values in parentheses were calculated with the same formula but using the sum of total isotope in samples 1-6 from both pulmonary artery and left atrium.

*For technical reasons the measurement of percent extraction was invalid after bypass.

(total of 12 samples before and 12 after bypass in each experiment) was determined specifically as described in Methods. \textsuperscript{3}H-NE in these experiments constituted 25.4 ± 0.8% (SE).
and 28.6 ± 2.1% of the total ³H before bypass and
23.6 ± 2.1% and 26.3 ± 0.9% after bypass. Corresponding figures for ¹⁴C-5-HT were
50.8 ± 3.4% and 63.8 ± 5.6% before bypass and
52.1 ± 6.3% and 56.4 ± 4.8% after bypass.

EXTRACTION OF ³H-WATER AND ¹⁴C-5-HT
To determine whether the more effectively
extracted amine in the present study, namely
5-HT, acted as a freely diffusible molecule,
pulmonary removal of ³H-water was com-
pared with that of ¹⁴C-5-HT in two patients.
Water was chosen as a freely diffusible
molecule that rapidly crosses pulmonary
capillary membranes (17). In these experi-
ments, the technique of isotope administra-
tion, sampling, and analysis was as described
above (Methods). Data from these experi-
ments are presented in Table 3. Water
behaved in a manner qualitatively different
from 5-HT in this system. 5-HT extraction
after bypass was increased in both patients,
but apparent ³H-water extraction decreased
after bypass. A negative percent extraction
of water in one patient (J.O'K.) after bypass
resulted when five, but not when six, segments
were used to calculate total isotope extracted
by the lungs (Table 3).

Discussion
In the present study, it would have been
desirable, on theoretical grounds, to measure
isotope concentration in blood withdrawn
from both sampling sites until radioactivity
had reached background levels. If this were
possible, comparison of the integral of total
isotope in blood before and after its passage
through the lung would have yielded a true
measure of pulmonary extraction. Unfortunately,
this is not feasible because the duration of blood withdrawal must be suffi-
ciently short to avoid significant isotope recirculation. For this reason the withdrawal
period was always less than 35 seconds from
the end of isotope injection.

Data in the present study were derived by
measurement of total isotope in blood. This
radioactivity could be associated with amine
or metabolites. Within this context, it is
important to emphasize that, since blood
samples were withdrawn 30-35 seconds after
amine injection, any intrapulmonary metabo-
lism (and subsequent loss of radioactive
metabolite into the vascular space) must have
occurred within this brief period. It is unlikely
that such metabolism, if it occurred, could be
extensive. Accordingly, we believe that mea-
urement of total isotope accurately reflects
amine concentration in blood. On the basis of
animal experiments, it is known that, follow-
ing perfusion of lung with either amine,
metabolites of both ¹⁴C-5-HT (7) and ³H-NE
(6) are formed and released into the vascular
space of lung. If any metabolites were also
released from the lung in our study, this
radioactivity would of course increase the
total withdrawn from the left atrium and
would thus result in underestimation of amine
extraction by lung. In our work, the extent of
metabolic conversion by lung per se cannot be
measured, since NE in particular may be
extensively destroyed in man by blood-borne
enzymes (18). It is also likely that consider-
able degradation of radioactive NE and 5-HT
occurred in withdrawn blood during the delay

<table>
<thead>
<tr>
<th>Patient</th>
<th>¹⁴C-5-hydroxytryptamine Before bypass (%)</th>
<th>After bypass (%)</th>
<th>³H-water Before bypass (%)</th>
<th>After bypass (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.J.</td>
<td>28.2 (30.0)</td>
<td>36.1 (28.1)</td>
<td>46.1 (47.8)</td>
<td>8.1 (0)</td>
</tr>
<tr>
<td>J.O'K.</td>
<td>69.5 (65.3)</td>
<td>72.0 (76.5)</td>
<td>28.0 (15.2)</td>
<td>-7.2 (9.9)</td>
</tr>
</tbody>
</table>

Values are percent extraction calculated according to formula \((\text{P.A.} - \text{L.A.})/\text{P.A.}) \times 100\), where \text{P.A.} = \text{sum of total isotope in samples } 1-5 \text{ withdrawn from pulmonary artery and L.A.} = \text{sum of total isotope in samples } 2-6 \text{ withdrawn from left atrium. Percent extraction values in parentheses were calculated with the same formula but using the sum of total isotope in samples } 1-6 \text{ from both pulmonary artery and left atrium.}

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(20 minutes) before deproteinization of blood. Thus, determination of tritium associated specifically with NE or its metabolites would reflect metabolism of the amine within the lung and also enzymatic and nonenzymatic degradation that occurred in the blood. In support of this reasoning, it was found that only 26% (average) of total 3H was associated with NE; the corresponding figure for 5-HT was 56% of total 14C (see Results).

It is not clear from these data whether use of five or six segments is more appropriate in calculating total isotope withdrawn from each sampling site. Withdrawal of blood was completed in approximately 30 seconds. Since blood at both sampling sites was divided into six segments, each was withdrawn during an interval of approximately 5 seconds. Assuming that this interval is the maximum circulation time from pulmonary artery to left atrium (19) then it is appropriate, in comparing total isotope withdrawn from both sampling sites, to neglect the sixth sample withdrawn from the pulmonary artery and the first from the left atrium. Thus we assume that isotope represented by the last sample from the pulmonary artery has not yet passed to the left atrium before sampling is completed. Also, the first sample from the left atrium reflects isotope which has not been sampled from the pulmonary artery. Table 2 shows that use of five, rather than six, samples in calculation significantly altered the calculated percent extraction of 14C-5-HT and 3H-NE: this difference was not observed in data obtained after bypass (Table 2). Whether extraction values calculated with five or six segments represent the more accurate estimate depends on right ventricular output and pulmonary circulation time when blood is withdrawn.

These data indicate that 14C-5-HT is more effectively removed during its passage through the pulmonary vascular bed of man than is 3H-NE (Table 2). Comparison of 5-HT and NE removal in each patient showed a statistically significant difference both before (P < 0.005) and after (P < 0.01) bypass. Another indication of the relatively greater removal of 5-HT is that the ratio of 14C to 3H in left atrial blood was always lower than that in pulmonary arterial blood. Greater removal of 5-HT could result from either increased uptake by lung tissue or increased binding of the amine to platelets which, in turn, might remain within the lung. The latter is unlikely, since platelet binding sufficient to explain the increased 5-HT removal observed seems unlikely within the 30-35 seconds of withdrawal.

The magnitude of pulmonary extraction of NE observed is comparable to that reported by others. Biron et al. (20) in a preliminary study of patients undergoing diagnostic cardiac catheterization noted that 30% of injected NE was inactivated by the lung. This was based on comparison of pressor activity of NE injected on the right of the heart (and thus also traversing the coronary system) with that injected on the left. Biron (personal communication) subsequently reported a mean percent extraction of 17% (range 0-35%) for NE when the contribution of cardiac stimulation to the pressor response, which was used as the basis for measurement of pulmonary extraction, was taken into account. Our figure for mean NE extraction before bypass is 23.3 ± 4.8% (Table 2). Thus, our direct measurement and the indirect estimate of Biron et al. (20) are in good agreement. Pulmonary inactivation of NE estimated at 30% in dog and cat (21) and at 28-38% in rabbit (9) is in a similar range.

Before bypass, 5-HT extraction averaged 65.0 ± 3.7% (Table 2) and was always much greater than that of NE in all nine patients. These data represent the first direct demonstration that pulmonary 5-HT extraction occurs in man. As in the case of NE, the magnitude of 5-HT removal in man is similar to that in other species (4, 7).

In comparing the extraction of NE and 5-HT before and after bypass (Table 2), the role of blood flow during sampling must be examined in relation to calculated amine removal. If cardiac output were decreased immediately after bypass, then removal of a fixed volume of blood would mean that relatively more isotope was withdrawn at the
right than at the left of the lungs. Since cardiac output was not measured directly in these patients, we used an indirect estimate of blood flow rates before and after bypass. Total isotope withdrawn from the pulmonary artery was expressed as a fraction of the total isotope injected in each case. Assuming that (1) no uptake or constant uptake of isotope occurred between the injection site and the heart and (2) there was complete mixing of isotope before sampling at the pulmonary arterial site, then the withdrawal fraction (total isotope withdrawn from pulmonary artery divided by total isotope injected) is a function of right ventricular flow, i.e., cardiac output. Furthermore, the ratio of withdrawal fraction before bypass to withdrawal fraction after bypass should be unity if cardiac output is unchanged. In all but one case, this ratio was less than 1, ranging from 0.26 to 0.72 for 5-HT and 0.37 to 0.87 for NE (Table 4). Thus there appeared to be a drop in pulmonary artery blood flow after bypass. In the patient (L.J.) with a ratio of withdrawal fraction before bypass to that after bypass of 1.22 (for 14C-5-HT), the heart was extremely irritable before bypass and lidocaine was used to control episodes of ventricular tachycardia. It is therefore likely that cardiac output in this patient was improved after bypass when no arrhythmia was present. Yet even in this patient 5-HT extraction increased from 28% before bypass to 36.1% after bypass (Table 3).

To determine whether any relationship existed between the magnitude of alteration in pulmonary removal and the changed pulmonary arterial blood flow, the statistical correlation between the ratio of withdrawal fraction before bypass to that after bypass and the ratio of percent extraction before bypass to that after bypass (Table 4) was calculated. The correlation coefficient (r) for 14C-5-HT was 0.137 (n = 9) and that for 3H-NE was 0.465 (n = 7). Since neither value was significantly different from zero, it may be concluded that there was no correlation between pulmonary arterial blood flow and calculated 5-HT or NE extraction. Accordingly, the increased extraction of both 5-HT and NE immediately after bypass (Table 2) was not due to changes in pulmonary blood flow.

Pulmonary blood volume may have increased after bypass as a result of vasodilatation. Even if this had occurred, however, it cannot explain the observed increase in pulmonary amine extraction. If pulmonary blood volume had increased, then left atrial blood isotope concentration should have increased less rapidly than observed before bypass. In fact, the opposite occurred.

There was no obvious relationship between either the magnitude of amine extraction or

### TABLE 4

<table>
<thead>
<tr>
<th>Patient</th>
<th>14C-5-hydroxytryptamine</th>
<th>3H-Norepinephrine</th>
<th>14C-5-hydroxytryptamine</th>
<th>3H-Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$F_b$</td>
<td>$F_a$</td>
<td>$F_b/F_a$</td>
<td>P.E.$b$/P.E.$a$</td>
</tr>
<tr>
<td>E.R.</td>
<td>26.4</td>
<td>40.9</td>
<td>0.65</td>
<td>0.75 (0.77)</td>
</tr>
<tr>
<td>A.P.</td>
<td>52.1</td>
<td>107.2</td>
<td>0.26</td>
<td>0.75 (0.67)</td>
</tr>
<tr>
<td>R.K.H.</td>
<td>44.1</td>
<td>148.1</td>
<td>0.30</td>
<td>0.63 (0.55)</td>
</tr>
<tr>
<td>J.P.</td>
<td>98.9</td>
<td>161.1</td>
<td>0.61</td>
<td>0.86 (0.49)</td>
</tr>
<tr>
<td>M.A.</td>
<td>79.9</td>
<td>110.9</td>
<td>0.72</td>
<td>1.05 (1.04)</td>
</tr>
<tr>
<td>L.J.*</td>
<td>153.2</td>
<td>253.5</td>
<td>1.22</td>
<td>0.78 (1.07)</td>
</tr>
<tr>
<td>J.O'K*</td>
<td>57.0</td>
<td>119.8</td>
<td>0.47</td>
<td>0.97 (0.85)</td>
</tr>
<tr>
<td>H.H.</td>
<td>34.9</td>
<td>69.2</td>
<td>0.51</td>
<td>0.79 (0.74)</td>
</tr>
<tr>
<td>M.L.</td>
<td>36.2</td>
<td>87.3</td>
<td>0.41</td>
<td>0.85 (0.83)</td>
</tr>
</tbody>
</table>

$F_b =$ fraction ($\times 10^{-6}$) of injected dose withdrawn from pulmonary artery before cardiopulmonary bypass, and $F_a =$ that withdrawn after bypass. P.E.$b$/P.E.$a$ = percent pulmonary extraction before cardiopulmonary bypass, and P.E.$a$ = that after bypass. P.E.$b$/P.E.$a$ was calculated using five samples, as explained in Table 2; values in parentheses were calculated using six samples, as explained in Table 2.

*Patients to whom 14C-5-HT and 3H-water were administered. See Table 3.

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the quantitative enhancement of the process and the duration of total bypass (Table 1). In considering changes in pulmonary amine extraction after bypass, the absolute value is likely to be less significant, biologically, than the magnitude of change relative to the average extraction in each patient. To emphasize this fact, the statistic \( \Delta E/E \) (where \( \Delta E \) is the percent extraction after bypass minus the percent extraction before bypass and \( E \) is the average extraction for the patient under study) was calculated. In six of seven patients, this value for 5-HT was positively correlated with time on bypass (\( r = 0.784, P < 0.025 \)). This observation suggests that some link may exist between magnitude of change in pulmonary 5-HT extraction and duration of cardiopulmonary bypass.

Although our work demonstrates conclusively the existence in man of 5-HT and NE inactivation by the lung, the physiological or pathophysiological significance of the inactivation is unknown despite earlier speculation (8, 10-12). Equally unclear is the effect of increased removal of these amines, particularly in the case of NE, after total cardiopulmonary bypass. However, if the marked elevation of NE extraction persists, one possible consequence is that intravenous administration of this amine as a vasopressor agent may have much less effect on arteriolar tonus than anticipated, because of unexpectedly high pulmonary clearance.

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References


20. BIRON, P., BOILEAU, J.C., AND CAMPEAU, L.: Norepinephrine inactivation in the pulmonary

Books Received

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