Some Circulatory Effects of 5-Hydroxytryptamine in Man

By P. Harris, M.D., H. W. Fritts, Jr., M.D., and A. Courand, M.D.

VASOACTIVE drugs have in general proved to have much weaker effects on the pulmonary circulation than on the systemic circulation. However, 5-hydroxytryptamine (5-HT) has been thought to be an exception because it causes a distinctive rise in the pulmonary vascular resistance both in intact animals1-6 and in perfused lungs.7-10 Since this substance circulates in the human body, the possibility arises that 5-HT might control the pulmonary vascular resistance—a possibility strengthened by the observation that the concentration of the agent diminishes during its passage through the pulmonary vessels.7 In the present study, this hypothesis was tested in 10 patients with normal hearts and minimal healed tuberculous lesions of the lungs.

Methods

5-HT was given in the form of the creatinine sulfate salt dissolved in 0.9 per cent saline. The doses specified in table 1 have been expressed in terms of 5-HT base.

All of the subjects were in a fasting and basal state, and all were studied in the supine position. In 7 subjects the effects of continuous infusions of 5-HT were observed. For this purpose a double-lumen catheter with only 5-cm. distance between the openings was advanced until the proximal opening lay in the main pulmonary artery just beyond the pulmonic valve. 5-HT was administered by a constant-infusion pump via the side opening of the catheter, while measurements of pressure and samples of blood were obtained from the opening at the end. An indwelling needle in the right brachial artery provided a means of obtaining blood samples and measuring pressures in the systemic circulation.

The patient breathed air through a mouthpiece connected to an open breathing circuit. The pressures in the pulmonary and brachial arteries were measured 6, 8, and 10 minutes after the mouthpiece was inserted, and the cardiac output was measured by the Fick principle at the end of the ninth minute. Two minutes later, the infusion of 5-HT was started. The pressures were measured after 2 and 4 minutes of infusion, and the cardiac output was measured after 5 minutes. The infusion was then stopped and in most of the patients after 3 minutes the pressures were measured again.

In 3 subjects, doses of 5-HT of 1, 2, and 4 µg. per Kg. were rapidly injected into the right atrium through a cardiac catheter. In these subjects a second catheter was placed in the pulmonary artery and the pressures in the pulmonary and brachial arteries were recorded during the injection.

Results

The results of the continuous infusions of 5-HT are presented in tables 1 and 2. Only 1 subject (M.M.) showed an unequivocal rise in pressure in the pulmonary artery during the infusion, which was accompanied by a rise in brachial arterial pressure. In another subject (L.Z.) there was some rise in both pulmonary and systemic arterial pressures during the second infusion. The most frequent response was a rise in pulse rate. There was no consistent alteration of cardiac output, ventilation, or arterial oxygen saturation. The oxygen uptake showed considerable variation; the respiratory quotient showed little change.

The single rapid injections of 1 and 2 µg. per Kg. of 5-HT base into the right atrium of 2 subjects caused no alteration in the pressure in the pulmonary or brachial arteries. The rapid injection of 4 µg. per Kg. into the right atrium of the third subject had such profound effects that the study was discontinued (fig. 1.).

Five seconds after injection, the subject started to cough. Between the ninth and twelfth seconds after the injection, there was no ventricular complex on the electrocardiogram and the pressure in both the brachial and pulmonary arteries fell greatly. During this 3-second interval, however, 1 P wave was

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Cardio-Pulmonary Laboratory of the First Medical and Chest Services, Columbia University Division, Bellevue Hospital, New York, N.Y.

Supported by a research grant (H-2001 (C)) from the National Heart Institute, National Institutes of Health, U.S. Public Health Service.
Table 1
Effects of an Intravenous Infusion of 5-Hydroxytryptamine (5-HT) on the Circulation in Seven Human Subjects*

<table>
<thead>
<tr>
<th>Case</th>
<th>Dose of 5-HT (μg./Kg./min.)</th>
<th>Time</th>
<th>PA (mm. Hg)</th>
<th>BA (mm. Hg)</th>
<th>HR (L./min./M.²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.R.</td>
<td>2.4</td>
<td>Before</td>
<td>24/6,14</td>
<td>139/82,105</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>24/7,13</td>
<td>137/81,106</td>
<td>59</td>
</tr>
<tr>
<td>T.B.</td>
<td>3.0</td>
<td>Before</td>
<td>17/7,10</td>
<td>138/93,111</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>16/7,10</td>
<td>136/92,110</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>14/5,8</td>
<td>137/95,112</td>
<td>121</td>
</tr>
<tr>
<td>M.M.</td>
<td>4.5</td>
<td>Before</td>
<td>27/12,18</td>
<td>128/75,98</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>33/17,23</td>
<td>158/91,112</td>
<td>73</td>
</tr>
<tr>
<td>T.H.</td>
<td>4.5</td>
<td>Before</td>
<td>35/13,22</td>
<td>146/88,119</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>34/13,22</td>
<td>152/92,121</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>32/11,21</td>
<td>153/91,122</td>
<td>75</td>
</tr>
<tr>
<td>W.M.</td>
<td>6.5</td>
<td>Before</td>
<td>20/8,13</td>
<td>126/78,99</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>20/9,14</td>
<td>126/78,99</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>22/9,14</td>
<td>131/79,100</td>
<td>99</td>
</tr>
<tr>
<td>L.Z.</td>
<td>1.85</td>
<td>Before</td>
<td>18/4,11</td>
<td>114/67,88</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>15/3,9</td>
<td>114/67,86</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>14/2,9</td>
<td>93/55,73</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>18/4,12</td>
<td>107/68,87</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>18/4,11</td>
<td>102/64,83</td>
<td>70</td>
</tr>
<tr>
<td>J.S.</td>
<td>4.5</td>
<td>Before</td>
<td>19/6,12</td>
<td>138/75,101</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>17/8,12</td>
<td>136/79,103</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>18/9,13</td>
<td>130/75,99</td>
<td>89</td>
</tr>
<tr>
<td>5.5</td>
<td>2.7</td>
<td>Before</td>
<td>18/7,12</td>
<td>133/78,101</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>21/8,13</td>
<td>132/78,103</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>20/6,12</td>
<td>132/77,100</td>
<td>86</td>
</tr>
</tbody>
</table>

*The symbols used in tables 1 and 2 are defined as follows: PA, pulmonary arterial pressure; BA, brachial arterial pressure; HR, heart rate; Q, cardiac output; Vₑ, volume of gas expired per minute (BTPS); Vₒₑₑ, volume of oxygen taken up per minute (STPD); Rₑ, respiratory exchange ratio; CAₒₑₑ, arterial blood oxygen content; Cᵥₒₑₑ, mixed venous blood oxygen content; Sₐₒₑₑ, arterial blood oxygen saturation; CAPₒₑₑ, arterial blood oxygen capacity.

Discussion

The normal rate of excretion of 5-hydroxyindoleacetic acid in the urine is said to be 2.9 mg. per day, while patients with malignant carcinoid may excrete up to 900 mg. per day. If the excretion is taken as a measure of the average rate of production of 5-HT in the body, it will be seen that the rates of infusion of 5-HT into the circulation in this present study were greatly in excess of its average physiologic rate of production but within the range found under pathologic conditions.

At this rate of infusion, there was no con-

Circulation, Volume XXI, June 1940

recorded, which was associated with a pressure wave in the brachial and pulmonary arterial tracings. The period of asystole was followed by bradycardia, which gave way to a tachycardia by the twentieth second after the injection. By this time, the pulmonary arterial pressure had risen to a figure of 27/16 mm. Hg from a control value of 19/8 mm. Hg and the pressure in the brachial artery had risen to such an extent that only the diastolic value was recorded. During the succeeding 4 minutes these pressures gradually returned to their normal values.
sistent effect on the pressures in the pulmonary or brachial artery. The one time unequivocal changes in pressure were recorded, they were observed both in the pulmonary and brachial arteries. We were not able, therefore, to find a dosage of the drug that would influence the pulmonary arterial pressure without altering the brachial arterial pressure. Although the rise in pulmonary artery pressure in subject M.M. was not accompanied by any change in cardiac output, it is not permissible to assume that it was due to an increased pulmonary vascular resistance in the absence of any knowledge of the left atrial pressure. This is more particularly so, since there was evidence of systemic vasoconstriction that might have displaced blood from the systemic to the pulmonary circulation.

Of the other functions measured, the constant infusion of 5-HT caused no consistent change in cardiac output, arterial oxygen saturation, or ventilation. The only consistent finding was that the heart beat a little more rapidly during the infusion.

These observations are different from those made by Rudolph and Paul, who studied the effects of sustained infusion of 5-HT in dogs. These authors found a 2- to 3-fold rise in the pulmonary arterial pressure with an eventual lowering of the systemic arterial pressure and a consistent rise in cardiac output averaging 60 per cent. The doses used by Rudolph and Paul were considerably greater than those used in these studies, the lowest rate of infusion being 9 μg. per Kg. per minute, the usual being 65 μg. per Kg. per minute of 5-HT base. Borst, Berglund, and McGregor, however, infused 5-HT into 1 branch of the pulmonary artery in dogs at a rate of 1 to 14.6 μg. of base per Kg. per minute and found unequivocal evidence of an increased vascular resistance in the lung to which the drug had been given at all levels of dosage. These observations suggest that there is a species difference in the response to this substance.

Whether this difference lies in the responsiveness of the pulmonary arteries has now become doubtful since the work of Kniseley, Wallace, and Addison, which appeared after our studies were completed. These authors showed by direct observation that the increased pulmonary vascular resistance ob-
served following the intravenous injection of 5-HT in rabbits, cats, and dogs was associated with the lodging of many small emboli in the pulmonary arteries. The material composing the emboli soon broke up and passed through the capillaries, after which the pulmonary vascular resistance returned to normal. The action of 5-HT may therefore be primarily or entirely a mechanical one, and the difference between dogs and men may lie in the chemical composition of the blood rather than in the medial musculature of the pulmonary arteries. The lack of effect of infusions of 5-HT on the human pulmonary circulation is consistent with the absence of pulmonary hypertension in patients with malignant carcinoid.13, 14

As far as the systemic circulation is concerned, Page and McCubbin15 found, like Rudolph and Paul,5 that the effect of a continuous intravenous infusion of 5-HT in dogs and cats was usually a sustained lowering of arterial pressure. In neurogenic hypertensive dogs this hypotensive effect was more evident, whereas, in normal dogs that had received ganglion-blocking agents, 5-HT caused a rise in arterial pressure. By these and other experiments,16 these authors distinguished between a direct action of 5-HT on the arterial vessels, which caused constriction, and an indirect vasodilator action of the drug due to its property of decreasing neurogenic tone. In patients with benign hypertension, however, sustained intravenous infusions of 5-HT at rates of 0.2 to 1.5 mg./min. raised the systemic arterial pressure.15 Magalini, Stefanini, and Smith17 infused 5-HT at a rate of 144 μg. base/min. for 30 minutes into a peripheral vein of 1 human subject and observed local venoconstriction but no alteration in the systemic arterial blood pressure. Similar results were obtained by Hollander, Michelson, and Wilkins18 with the intravenous infusion of 4.4 to 21.7 μg. of 5-HT base per minute. Spies and Stone19 injected 5-HT intravenously into human subjects in doses of 0.1 to 2.2 mg. of base given over 5 to 300 seconds. Whenever more than 217 μg. of base was injected, systolic arterial blood pressure as measured by a cuff-sphygmomanometer rose. These doses also caused pains in the abdomen and other sensations that were absent in our subjects. The effects of arterial infusion of 5-HT have been studied by Haddy, Fleischman, and Emanuel21 in the isolated foreleg of the dog. Large arteries and veins constricted but small vessels dilated, the total vascular resistance not being substantially altered. Roddie, Shepherd, and Whelan20 found that the infusion of 0.11 to 7 μg. of 5-HT base per minute into the brachial artery in man caused a fall in blood flow through the forearm and hand and a flushing of the skin.

The mechanism underlying the tachycardia observed in our subjects is not clear. It is tempting to attribute such an effect to an alteration of the sensitivity of the baroreceptors of the carotid sinus due to the local action of 5-HT. There is little experimental evidence in favor of such an action, however, except for a report by Gordon, Haddy, and Lipton,22 that during the infusion of 5-HT, norepinephrine causes a tachycardia instead of the usual bradycardia.

In animals, a qualitative difference has been found between the effects of short intravenous injections and of continuous infusions of

---

*Figure 1*

Effect of a rapid injection of serotonin on brachial arterial (BA) and pulmonary arterial (PA) pressures. For discussion, see text.
5-HT. A single injection is followed by a rapid rise in the pulmonary arterial pressure. The response of the systemic arterial pressure is more complex. Working with vagotomized cats under chloralose, Reid found that the intravenous injection of 5-HT caused an initial fall in the systemic arterial pressure followed by a rise and then a prolonged fall. The initial fall in systemic arterial pressure coincided with the rise in pulmonary arterial pressure and fall in left atrial pressure. After injection into a pulmonary vein, the initial fall in systemic arterial pressure was absent and the rise in pulmonary arterial pressure was slight and delayed. Reid therefore thought that the initial fall in systemic arterial pressure was caused by pulmonary vasoconstriction. Others reached a similar conclusion.

Comroe et al., however, found that the rapid intravenous injection of 5-HT into cats with intact vagi under chloralose caused bradycardia, systemic hypotension, and apnea, such as is found in the Bezold reflex. In addition there was a rise in right ventricular pressure, which was interpreted as being due to pulmonary vasoconstriction. Atropine and vagotony blocked the bradycardia and hypotension but did not influence rises in right ventricular and vena caval pressures. These authors found that the Bezold-like reflex could occur before the appearance time of tracer substances in the aorta. The same reflex could also be elicited, however, by injections into the left ventricle or ascending aorta; it was concluded that receptors were stimulated in both the pulmonary and the coronary circulation.

The sequence of events in figure 1 indicates that the initial fall in brachial arterial pressure was the first change to occur; its rapid time of appearance after injection might be construed as evidence of its reflex nature. The rise in pulmonary arterial pressure occurred later, when it was in fact accompanied by a rise in pressure in the brachial artery. This rise in pulmonary arterial pressure may have been due to a sustained increase in pulmonary vascular resistance or could have been caused by an increase in pulmonary blood volume arising from vasoconstriction in the systemic circulation. In this subject dilution curves of T 1824 injected into the right atrium may provide useful information about the mechanism underlying the cardiopulmonary events. In 3 such injections the average value for the appearance time of dye in the brachial artery was 7.5 seconds. Thus coughing, which started 5 seconds after the injection of 5-HT, presumably arose from receptors in the pulmonary circulation, while the bradycardia and hypotension, which appeared at 9 seconds, could have been caused by a reflex arising from receptors in the coronary circulation. There was no respiratory record in this study, but the pulmonary and brachial artery pressure tracings show coughing only between the fifth and eighth second. Whether apnea occurred at the time of ventricular arrest is not known, but immediately thereafter respiratory fluctuations could be seen on the pressure tracings.

Hollander, Michelson, and Wilkins, using rapid intravenous injections of 0.11 to 0.87 mg. of 5-HT base in man, noted a variable response in the systemic arterial pressure but nearly always a transient increase in the rate and depth of breathing. The pulmonary arterial pressure was not affected. They did not encounter any such alarming episode as occurred in our subject.

Summary

Continuous infusions of small quantities of 5-hydroxytryptamine (5-HT) were made into the pulmonary artery in 7 human subjects. In only 1 instance was there an unequivocal rise in pressure in the pulmonary artery and this was accompanied by a rise in brachial arterial pressure. The most consistent effect of the drug was to raise the heart rate. There was no effect on the cardiac output.

Single rapid injections of 5-HT were made into the right atrium in 3 other subjects. In 1 of these subjects the injection of 4 µg per Kg. caused transient ventricular arrest and systemic hypotension followed by a sustained rise in pressure in the pulmonary and brachial arteries. The results of this study were thought to indicate the presence of a Bezold-like reflex. The rapid injection of 5-HT was therefore thought to be dangerous and the investigation was discontinued.

Circulation, Volume XXI, June 1960
Summario in Interlingua

Continue infusiones de micre quantitates de 5-hydroxytryptamina (5-HT) esseva effectuate in le arteria pulmonar de 7 subjectos human. Un augmento inequivoc del tension pulmonar-arterial esseva constata post ille tractamento in solmente un del casos, e hie le augmento del tension pulmonar-arterial esseva accompaniate de un augmento del tension brachio-arterial. Le plus uniforme effecto del droga esseva le facto che illo augmentava le frequentia cardiace. Nulle effecto super le rendimento cardiace esseva notate.

Simple injectiones rapide de 5-HT esseva effectuate in le atrio dextere de 3 altere subjectos. In 1, le dose de 4 μg per kg de peso corporee causava un transiente arresto ventricular e hypotension systemique sequite per un perdurative augmento del tension in le arterias pulmonar e brachial. Es opinate che le resultatos de iste studio indica le presentia de un reflexo del typo Bezold. Isto significarea che le injection rapide de 5-HT esseva periculose. Per consequente le investigacion esseva interrupte.

References
Some Circulatory Effects of 5-Hydroxytryptamine in Man
P. HARRIS, H. W. FRITTS, JR. and A. COURNAND

Circulation. 1960;21:1134-1139
doi: 10.1161/01.CIR.21.6.1134

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/21/6/1134

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/