CARDIAC OUTPUT IN DOGS DURING INFUSION OF BETAHISTINE. Smith et al. 257

By exclusion then, it seems that the main cause of brain infarcts may be sudden vascular occlusion and not stenosis. Most of the occlusions may be caused by thromboemboli, as suggested previously. 1,2 However, it should be noted that some of the occlusions may be caused primarily by rupture of atherosclerotic plaques, which are easily overlooked when secondary thrombosis has occurred. 3 Furthermore, many of the vascular occlusions in the deep-seated small infarcts of hypertensive subjects apparently are caused by degenerative changes in the vascular walls and not by primary thrombi. 4

References

SummarY Cardiac output (CO), arterial blood pressure (ABP), heart rate (HR), blood gases and blood flow (BF) to the brain, heart, kidney and skeletal muscles and other cephalic tissues in five dogs were studied before and at 30 minutes of betahistine infusion (0.12 to 0.2 mg per minute per kilogram). The particle distribution method using radioactive labeled 155,157,159,161 Co (15 μCi) and 158,160,162,164 Sr (15 μCi) microspheres was utilized to quantitate and assess BF and CO. In the five dogs, the increase in CO averaged 20.8%, ABP remained constant, and HR increased in all but one exception where it decreased slightly concomitant with a decrease in Paco2 Brain BF increased (+ 29.6%) in the dogs whose Paco2 remained constant. The BF increased to the heart (25.4%) and skeletal muscle (80%), while BF to the kidney and other tissues did not change. The change in HR appears to account for the change in CO. The dilating effect of betahistine on blood vessels, in the skeletal muscle, brain and heart could reduce peripheral resistance and decrease ABP. Thus, the increase in HR may be mediated through baroreceptor mechanisms rather than by a direct effect of betahistine. In addition, a decrease in Paco2 is more effective for decreasing cerebral BF than betahistine is for increasing blood flow.

WE HAVE STUDIED the effect of betahistine hydrochloride on the distribution of cardiac output (CO) in five dogs using the particle distribution method. This microsphere or particle distribution method has been previously used 5 to quantitate and assess organ and/or regional blood flow (BF) in different experimental animals. An earlier study 6 suggested that the vascular properties of betahistine may be similar to the properties of histamine. Various investigators, therefore, have examined hemodynamic changes during and after betahistine administration. After a single intravenous injection of betahistine (0.055 to 0.44 mg per kilogram) in dogs, Anderson and Kubicek 7 observed a decrease in arterial blood pressure (ABP) concomitant with a 54% increase in basilar artery blood flow using an electromagnetic blood flow transducer. Phillips 8 also using a bolus injection and flowmeter techniques in dogs, found a significant elevation in coronary blood flow (58.6% to 200%) with minor changes in heart rate (HR) and arterial blood pressure. The blood flow response tended to be dose dependent, increasing with larger doses. When betahistine (0.1 to 0.48 mg per kilogram per minute) was administered over a longer period of time, coronary blood flow increased five to six seconds after the beginning of the infusion. In a preliminary study in dogs, Dueland 9 suggested that CO increased following a four-hour infusion of betahistine during hemorrhagic shock. Kubicek and Anderson 10 found that 11 of 12 dogs recovered from induced hypovolemic shock after betahistine treatment, whereas 66% of the controls died. Studies in experimental animals to examine BF and hemodynamic changes in numerous organs and tissues simultaneously during betahistine administration have not been made. In this study we have determined the blood flows to major organs and tissues such as the brain, heart, kidney and skeletal muscle. The CO for each animal and the BF to other cephalic tissues were also calculated.

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Methods

Five dogs, four to six months old (9.5 to 15.6 kg), were anesthetized and maintained with sodium pentobarbital; all except one were placed on artificial respiration. Arterial blood pressure and heart rate were monitored via a branch of the right femoral artery. Left brachial and left femoral arteries were cannulated for reference blood flow sampling during the injection of the microspheres. The left ventricle was catheterized via the right brachial artery for injecting the microspheres. Readings for PaCO2, PaO2, and pH were taken from an arterial blood sample after cannulation and before the injection of the microspheres. In four dogs, 1.6 to 3.9 × 10^14 Ce labeled microspheres (diameter of 16.0 μ ± 4.4) were injected before betahistine infusion, whereas in the remaining dog, 5.6 × 10^15 Ce microspheres (8.6 μ ± 0.8) were injected. After the first injection of microspheres, betahistine, (2 mg per milliliters) was infused at a rate to provide a dosage of 0.2 mg per kilogram per minute in four dogs and 0.12 mg per kilogram per minute in the other dog. At 30 minutes, a known quantity of Sr microspheres (14.9 μ ± 4.9) was injected concomitant with the reference flow sampling. The dogs were killed with a saturated potassium chloride injection into the femoral vein. The entire brain, heart, kidneys, salivary glands and dental pulps of the canine teeth were removed. The lungs also were removed and samples taken from the various lobes to assess microsphere recirculation. Representative tissue samples were taken from skeletal muscle (masseter and temporal) and tongue. The activities of each isotope for all the organ and tissue samples were determined using a dual window gamma scintillation counter. BF and fractional uptake per unit weight for each tissue sample and for each isotope were calculated by the particle distribution method and analyzed by the paired Student’s t test. The CO for each dog, the total organ blood flow and the percent of CO to each organ were calculated.

The validity of using the radioactive labeled microspheres to assess regional blood flow to various tissues and organs in experimental animals has been established by ourselves and others.1, 2, 3, 4, 6-12 The flow (Fi) to any organ or region (i) is equal to the quantity of radioactivity (Qi) found in the organ or region divided by the integral of the arterial concentration time curve of the isotope (∫ C(t) dt): i.e., F_i = Q_i / ∫ C(t) dt. The integral is equal to the amount of radioactivity collected in the reference blood sample divided by the flow at which the sample was taken. The cardiac output is simply the total quantity (Qo) of radioactivity injected divided by ∫ C(t) dt; therefore, the fractional uptake in a given organ or region is Qi/Qo.

Results

The general hemodynamic characteristics of the five dogs during control and the betahistine infusion can be contrasted (table 1). The cardiac output increased (%Δ ± SE) by 20.8%, P = 0.046. However, in the dog which was not artificially ventilated, the initial PaCO2 was 59.3 mm Hg compared to an average of 31.2 mm Hg for the other four. At 30 minutes of betahistine infusion, the PaCO2 had decreased to 42.4 mm Hg compared to an average of 29.7 mm Hg for the other four.

The average values from all five dogs for BF and percent distribution of CO to the brain, heart, kidney and skeletal muscle before and at 30 minutes of betahistine infusion are represented in table 2. The %Δ in cerebral blood flow and % CO averaged +3.2% and -16.3%, respectively, but were not significant when analyzed statistically for all five animals. However, considering the three dogs in which the PaCO2 did not change appreciably (table 3, Nos. 1, 4 and 5), cerebral blood flow increased 29.6%, but the % CO to the brain did not change. The mean % in blood flow to the cerebellar cortex, brainstem, pons and reticular formation, midbrain, thalamus, cerebral gray and white for these dogs with PaCO2 values between 27 and 30 mm Hg was +38.7% (range +2.3 to +92.3). In the two dogs in which PaCO2 decreased by 7% or more with initial values of 59.3 and 37.5 mm Hg (table 3), the %Δ in blood flow to these regions averaged -33.6 (range -12.5 to -55.7). In the dog (No. 3, table 3) whose PaCO2 decreased from 37.5 to 34.8 mm Hg, the %Δ in the regional brain blood flow was much less than that observed for the other dog. The percent change in blood flow to the heart averaged +25.4 (P = 0.058) while the % CO was +4.3 (NS). The %Δ in kidney blood flow and % CO averaged +5.7 and -12%, respectively. In skeletal muscle both the blood flow and the fractional uptake per gram increased significantly by about 80%. Blood flow to dental pulp, salivary glands and tongue was essentially unchanged. However, the increase in blood flow to the tongue (+16%) was not significant.

The radioactivity found in the lungs can be used as an indicator of the trapping efficiency of the peripheral circulation. Considering just the findings using the 15 μ spheres, the percent of the total activity injected found in the lungs appeared to be slightly less after betahistine infusion, averaging 4.84% and 3.06%, respectively. For the one dog in which 8.6 μ spheres were injected during control, 12.44% of the total quantity injected appeared in the lungs.

Discussion

Earlier studies have not clearly established the effect of betahistine on the cardiovascular dynamics. The microsphere method to quantitate local blood flow has been utilized to assess blood flow changes as well as changes in the % CO to the organs or tissues.1, 2, 3, 9, 10, 12, 13 In this study using five dogs, some significant hemodynamic changes do occur 30 minutes after intravenous infusion of betahistine (0.12 to 0.20 mg per minute per kilogram). The CO decreased slightly in one dog (No. 2, table 3) which was not

<p>| Table 1 Cardiovascular Status in Five Dogs During Control and at 30 Minutes Following Intravenous Infusion of Betahistine (0.12 to 0.20 mg/kg) |</p>
<table>
<thead>
<tr>
<th>Control</th>
<th>Betahistine</th>
<th>% diff.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (ml/min)</td>
<td>2,166 ± 163*</td>
<td>2,609 ± 232</td>
<td>20.8 &lt;0.05</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>118 ± 6</td>
<td>118 ± 6</td>
<td>-1.6 NS</td>
</tr>
<tr>
<td>Heart rate</td>
<td>147 ± 14</td>
<td>176 ± 10</td>
<td>24.5 0.12</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>36.8 ± 5.3</td>
<td>32.2 ± 2.9</td>
<td>-9.5 NS</td>
</tr>
</tbody>
</table>

*Mean ± SE.
artificially ventilated and Paco2 dropped from 59.3 to 42.4 mm Hg. Nevertheless, the average percent increase in CO for all five dogs was 20.8 (P slightly < 0.05, table 1), but excluding No. 2 the increase averages 27.2%. According to Tenney and Lamb,15 a Paco2 difference of 17 mm Hg (59 to 42) could account for 10% to 15% lower CO during the control period if the Paco2 had also been 42 mm Hg initially. Thus, one could conclude that betahistine would have increased CO in this dog had the Paco2 remained the same. The initial high Paco2 also could account for the low skeletal muscle blood flow observed during the control period. In this same dog the total brain blood flow as well as regional brain flow decreased significantly by about 50%, suggesting that the decreased Paco2 had more influence on changing brain flow than betahistine had to increase regional brain blood flow. Assuming that the skeletal muscle constitutes about 45% of the body weight, the increase in CO is more than adequate to account for an 80% increase in skeletal muscle blood flow.

Other hemodynamic variables also were observed during betahistine infusion. The arterial blood pressure in each animal did not change. In the dog not artificially ventilated, the heart rate decreased slightly. Assuming the stroke volume remains constant, this slight decrease can account for the slight decrease in CO. Thus, excluding this animal, the average increase in heart rate is 32.2% (P = 0.07) rather than 24.5% (P = 0.12), table 1. In the other four, the increase in heart rate can account for the increase in CO if stroke volume remains constant. The increase in CO may not be a direct effect of betahistine, but rather an indirect effect mediated through the baroreceptor mechanism. Betahistine may reduce total peripheral resistance particularly by dilating vessels in the skeletal muscles thereby tending to decrease systemic blood pressure. The blood pressure is then restored by an increase in heart rate via the pressor reflex, providing Paco2 remains constant.

The microsphere method has been used in other studies to compare changes in blood flow in dogs from a control status to some subsequent experimental condition.14,18 In some concomitant studies,17,18 the femoral and brachial arteries were also cannulated to obtain a reference flow sample. Cardiac outputs could be calculated from data obtained from each sample as well as the average (table 1) of the two for each dog. On the average, these cardiac outputs were within 4.4%. The number of spheres injected were sufficient to provide about 400 beads per sample needed to minimize the variability in the flow calculation.11 The fraction of the microspheres which are not trapped in the microcirculation is also an important consideration. Nearly 100% of the 15 μm microspheres are trapped by the coronary circulation.19 In some concomitant studies using dogs and injecting 15 μm and 8 μm microspheres simultaneously, the fractional entrapment of these two differently sized microspheres in various regions of the brain17 and other cephalic tissues18 sampled in this study was essentially identical. The lungs were removed in this study to assess the assumption of complete trapping of beads in the tissues sampled. The percent of the quantity injected appearing in the lungs averaged 3.95% (1.29 to 10.10) considering only the 15 μ. In a previous study using 15 μ spheres the average % CO was 4.97%,18 which is comparable to that observed by others.2 In another study using 25 μ spheres, the average was 1.5%.18 Since both bronchial blood flow and recirculation are involved, the recirculation may account for 3% to 4%. Grim and Lindseth,19 using microspheres having an average diameter of 12 μ, found that about 28% of them could be recovered in the venous blood from the jejenum of dogs. If the blood flow to the gastrointestinal (GI) tract of dogs is 18% to 21% of the CO and if about 15% of the 15 μ spheres can pass through the microcirculation, then 2% to 3% of the CO to the lung could be represented by recirculating microspheres from the GI tract. Thus, 98% to perhaps nearly 100% of spheres going to the tissues being examined are trapped during the first circulation. If the microspheres are distributed as blood flow as suggested by earlier work, then these findings provide further evidence of the effect that betahistine has on the cardiovascular system in dogs.

Betahistine appears to be capable of causing significant increases in cerebral blood flow in situations where Paco2 remains constant. This effect of betahistine can apparently be abolished by decreasing arterial PCO2, i.e., autoregula-

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**TABLE 3** Average Brain Blood Flow (ml/min/gm) and Arterial PCO2 During the Control and at 30 Minutes Following Intravenous Infusion of Betahistine (0.18 to 0.20 mg/min/kg) in Five Dogs

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Brain blood flow</th>
<th>Paco2</th>
<th>Brain blood flow</th>
<th>Paco2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Betahistine</td>
<td>Control</td>
<td>Betahistine</td>
</tr>
<tr>
<td>1</td>
<td>0.43</td>
<td>0.61</td>
<td>29.1</td>
<td>28.3</td>
</tr>
<tr>
<td>2*</td>
<td>1.56</td>
<td>0.81</td>
<td>52.1</td>
<td>42.4</td>
</tr>
<tr>
<td>3</td>
<td>0.45</td>
<td>0.34</td>
<td>37.5</td>
<td>34.8</td>
</tr>
<tr>
<td>4</td>
<td>0.37</td>
<td>0.48</td>
<td>29.6</td>
<td>28.6</td>
</tr>
<tr>
<td>5</td>
<td>0.35</td>
<td>0.41</td>
<td>28.6</td>
<td>27.0</td>
</tr>
</tbody>
</table>

*Not artificially respired.*
tion to Pco2 changes being intact. The results of this study should be considered if betahistine is being contemplated as a therapeutic agent in situations of focal cerebral ischemia. Recent studies by Spruill et al.10 showed that the frequency of transient ischemic attacks caused by vertebrobasilar insufficiency was not significantly changed for patients taking two 4-mg tablets of betahistine four times a day as compared to those patients taking a placebo. A concomitant rise in CO and HR may be undesirable in some patients with cerebrovascular and ischemic cardiac disease. It is possible that betahistine increases blood flow to normal regions of the brain with no effect on blood flow to ischemic areas. Further studies are needed to investigate and determine any potential beneficial role betahistine may have when given to patients with regional brain ischemia.

References


Cerebral Ischemia in Gerbils: Differential Vulnerability of Protein, RNA, and Lipid Syntheses

T. YANAGIHARA, M.D.

SUMMARY In order to compare the difference in the vulnerability of macromolecular syntheses, protein, RNA, and lipid syntheses were studied with ischemic brain tissue three hours following unilateral carotid ligation in gerbils. Precursor incorporation was measured in various subcellular fractions following in vitro incorporation with brain slices. There was marked inhibition of protein synthesis, but RNA and phospholipid syntheses showed little or no change. On the basis of available information on rapid deterioration of polysomal system for polypeptide synthesis, a hypothesis was proposed that messenger ribonucleic acid (RNA) at the polysomal level is promptly affected in this pathophysiological condition.

ALTHOUGH the alteration of the energy state has been studied extensively in anoxic or ischemic brain in the past, the effect of the depletion of oxygen and the energy source on the macromolecular metabolism has drawn relatively less attention. Since the macromolecules such as nucleic acids, protein, and lipid have a significant role in the cellular regulatory mechanism and are the constituents of various subcellular structures, understanding of the molecular mechanism leading to stroke and other neuropathologic processes may be an important aid in recognizing the mechanism for reversibility and irreversibility of each process. The rapid decline of protein synthesis after cerebral anoxia in vitro has been demonstrated as has the selective involvement of microsomal protein synthesis in comparison to ribonucleic acid (RNA) synthesis in the nuclei. Elsewhere it was suggested that messenger RNA is affected at either the stage of synthesis or transfer to cytoplasm, explaining the functional or structural alteration in polyribosomes. However, whether cerebral anoxia and ischemia result in the same morphologic or biochemical alteration or whether they manifest with different degradative processes...
Distribution of cardiac output in dogs during intravenous infusion of betahistine.
K A Smith and M W Meyer

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