METHOD FOR CONTROLLING VASCULAR RESPONSES

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Field of Search ...... 128/400, 303.1, 401, 24.1, 128/2 H

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Attorney, Agent, or Firm—Dawson, Tilton, Fallon & Lungmuss

ABSTRACT
A method for producing changes in systemic arterial blood pressure, cerebrospinal fluid pressure and heart rate, as well as producing selective brain hypothermia in animals by irrigating the nasal mucosa. The method includes locally applying a fluid to change the temperature of the region of the face and, hence, the blood drained by the angularis oculi and facial veins. Heat and cold produce opposite effects.

8 Claims, 12 Drawing Figures
**Fig. 4**

**TABLE I**

Summarization of pressure and heart rate changes and their time relationships

(CSFP = Cerebrospinal fluid pressure; ABP = Femoral arterial blood pressure)

<table>
<thead>
<tr>
<th>Number of Trials</th>
<th>Water Temp. Change</th>
<th>CSFP 1st</th>
<th>ABP 1st</th>
<th>CSFP 2nd</th>
<th>ABP 2nd</th>
<th>Heart Rate Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Dogs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethan Anesthesia</td>
<td>Cold to Hot</td>
<td>+3.0</td>
<td>+17.9</td>
<td>14.4</td>
<td>34.0</td>
<td>105.7</td>
</tr>
<tr>
<td></td>
<td>Hot to Cold</td>
<td>-2.5</td>
<td>-14.8</td>
<td>8.2</td>
<td>9.7</td>
<td>178.6</td>
</tr>
<tr>
<td>3 Dogs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metofane Anesthesia</td>
<td>Cold to Hot</td>
<td>+6.1</td>
<td>+18.5</td>
<td>20.6</td>
<td>18.2</td>
<td>289.3</td>
</tr>
<tr>
<td></td>
<td>Hot to Cold</td>
<td>-5.1</td>
<td>-18.8</td>
<td>80.5</td>
<td>24.0</td>
<td>497.1</td>
</tr>
</tbody>
</table>

1. Cold water temperature was 15°C and hot water temperature ranged from 45-48°C.
2. Time was measured from the instant the water temperature was changed.
3. Heart rate was not monitored in Experiment 8 (6 trials).
4. "+" = increase; "-" = decrease; and "0" = no change.
Temperature data for human subject study. All temperatures (columns 6-12) are in °C.

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Handedness</th>
<th>Sex</th>
<th>Vein</th>
<th>Before Thinking</th>
<th>Maximum Change During Thinking</th>
<th>Net Change for Column 9</th>
<th>Maximum Change After Thinking</th>
<th>Net Change for Column 9</th>
<th>Difference Between Before and After Thinking</th>
<th>Net Change for Column 11</th>
<th>11</th>
<th>12</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>R KD</td>
<td>P</td>
<td>L</td>
<td>34.8</td>
<td>↓ 0.3</td>
<td>↓ 0.5</td>
<td>↑ 0.4</td>
<td>↑ 0.5</td>
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<td>None</td>
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<td>2</td>
<td>R WF</td>
<td>*M</td>
<td>L</td>
<td>36.7</td>
<td>↓ 0.6</td>
<td>↓ 0.7</td>
<td>↑ 0.2</td>
<td>↑ 0.7</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R RD</td>
<td>*M</td>
<td>L</td>
<td>35.3</td>
<td>↓ 0.5</td>
<td>↑ 1.1</td>
<td>↑ 0.5</td>
<td>↑ 0.7</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R JD</td>
<td>*M</td>
<td>L</td>
<td>36.6</td>
<td>↓ 0.2</td>
<td>↑ 1.1</td>
<td>↑ 0.2</td>
<td>↑ 0.9</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>R GD</td>
<td>*F</td>
<td>L</td>
<td>30.7</td>
<td>↓ 0.9</td>
<td>↑ 1.4</td>
<td>↑ 1.1</td>
<td>↑ 1.7</td>
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<td>↑ 0.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>32.3</td>
<td>↓ 0.3</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R SL</td>
<td>*M</td>
<td>L</td>
<td>36.2</td>
<td>↓ 1.0</td>
<td>↓ 2.0</td>
<td>↑ 0.8</td>
<td>↑ 1.4</td>
<td>↑ 0.2</td>
<td>↑ 0.6</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td>A</td>
<td>35.4</td>
<td>↓ 1.0</td>
<td>None</td>
<td>None</td>
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<td>None</td>
<td>None</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>R KT</td>
<td>*F</td>
<td>L</td>
<td>35.0</td>
<td>↓ 0.6</td>
<td>↑ 0.8</td>
<td>↑ 0.9</td>
<td>↑ 1.2</td>
<td>↑ 0.3</td>
<td>↑ 0.4</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>A</td>
<td>34.3</td>
<td>↓ 0.2</td>
<td>↑ 0.3</td>
<td>↑ 0.6</td>
<td>↑ 1.9</td>
<td>↑ 0.3</td>
<td>↑ 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>R HB</td>
<td>**M</td>
<td>L</td>
<td>34.8</td>
<td>None</td>
<td>↑ 0.2</td>
<td>None</td>
<td>↑ 0.2</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>R</td>
<td>34.7</td>
<td>↑ 0.2</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>R JK</td>
<td>**M</td>
<td>L</td>
<td>34.7</td>
<td>↑ 0.3</td>
<td>↑ 1.5</td>
<td>↑ 0.6</td>
<td>↑ 1.3</td>
<td>↑ 0.3</td>
<td>↑ 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>33.4</td>
<td>↑ 1.2</td>
<td>↑ 1.3</td>
<td>↑ 1.9</td>
<td>↑ 0.3</td>
<td>↑ 0.1</td>
<td>↑ 0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:
1. R = right, L = left
2. * = thermistors placed under the skin along side the vein
   ** = thermistors placed on the skin surface over the vein
3. L = left angularis oculi vein
   R = right angularis oculi vein
   A = median antebrachial vein
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

(continued)

4. In laboratory with lights out and surroundings as quiet as possible.

5. \( \text{= temperature decrease; } \) \( \text{= temperature increase.} \)

6. Differences obtained from entries in columns 7 and 9.
An abstract of a paper given by us was published in The Physiologist, Vol. 10, No. 3, August, 1967, in which we reported achieving cooling of the brain of the canine by irrigating the alar folds of the maxilloturbinate with water having a temperature of 12.0°C. We reported that the venous blood passing from the alar folds into the cavernous sinus cooled the arterial blood passing to the brain by way of the latter sinus. This arterial blood absorbed heat from the brain after passing through components of the Circle of Willis and their distributing vessels. We postulated at the time of this work that two separate heat exchange mechanisms were involved — one, which we called the external heat exchange system, is located in the alar fold of the maxilloturbinate and cools blood which flows into the cavernous sinus by way of the angularis oculi vein, and the second, which we called the internal heat exchange system, is in the cavernous sinus where heat is transferred from the warm arterial blood destined for the brain to the cooler venous blood in the cavernous sinus.

In a subsequent article of Hayward and Baker entitled “A Comparative Study of the Role of Cerebral Arterial Blood in the Regulation of Brain Temperature in Five Mammals,” published in Brain Research, Vol. 16, p. 417, 1969, work was reported in this area on different species of mammals, and as a result, the authors classified their subjects into two broad categories: (1) those of the “internal carotid” artery type which includes the monkey and the rabbit and is characterized by having a single large vessel passing through the cavernous sinus thereby providing a flow pathway from the common carotid artery to the Circle of Willis; and (2) the “carotid rete” type which is characterized by having more than one communicating vessel from the common carotid artery to the Circle of Willis: (1) via the cavernous sinus as in the dog and sheep; and (2) in close proximity to a venous plexiform network in cats.

Based on their experiments, these researchers concluded that heat exchange occurs between the cooler venous blood in either the cavernous sinus (for the dog and sheep) or the venous plexiform network (in the case of the cat) and the warmer arterial blood only in those animals of the “carotid rete” type. Further, these researchers believed themselves to have demonstrated that for animals having a single internal carotid artery conducting blood through cavernous sinus, there was no heat exchange at the base of the brain. These studies concluded that this was a major difference between the two classifications. Persons skilled in the art will appreciate that when reference is made to an animal having a “single internal carotid artery” reference is made to only one of the two internal carotid arteries which, due to bilateral symmetry, occur in each such animal.

The results of our further experimental work on the physiological heat exchange systems for controlling the brain temperature of a dog are reported in an article appearing in the IEEE Conference Record, Fifth Annual Rocky Mountain BioEngineering Symposium 1968 entitled “Description of Two Physiological Heat Exchange Systems for the Control of Brain Temperature” and in an article published in the Journal of Applied Physiology, Vol. 27, No. 1, p. 18, 1969, entitled “Response of Veins Draining the Nose to Alar-Fold Temperature Changes in the Dog.”

SUMMARY

As a result of our experimentation, including work
performed on man and on horses each of which have a single large carotid artery leading from the common carotid artery and passing through the cavernous sinus to the Circle of Willis, we believe we have demonstrated that selective brain hypothermia can be induced by locally irrigating the surface area of the facial region or nasal passage drained by the angularis oculi and facial veins in animals with a single internal carotid artery, as well as those with a carotid rete, with cold water. The surface area as thus stated includes the facial skin in this region as well as the nasal mucosa, either one of which or both may be irrigated.

This, of course, is contrary to the conclusions reached by the distinguished researchers, Hayward and Baker, mentioned above. As a result of further experimentation with dogs, we have been able to induce changes in cerebrospinal fluid pressure, systemic blood pressure, and heart rate by irrigating the nasal mucosa. That is, we have been able to selectively increase the cerebrospinal fluid pressure, systemic blood pressure and heart rate by irrigating the tip of the nose with hot water; and we have produced reductions in cerebrospinal fluid pressure, systemic blood pressure and heart rate by irrigating the tip of the nose with cold water. Thus, we believe we have demonstrated a method of controlling blood flow to the brain of a mammal.

While not limiting the effect of our invention, we postulate that there are two principal physiological mechanisms or systems which have a bearing on the brain's temperature. One such system we call the venous temperature control system; and it regulates the cooling of the venous blood destined for the cavernous sinus. The second system we call the cardioarterial control system; and it acts in a manner to assist the venous temperature control system in regulating brain temperature. That is, when the venous control system has reached the limits of its capability to cool the venous blood, the cardioarterial system will further influence the rate of heat exchange occurring between arterial and venous blood in the cavernous sinus by apparently altering arterial blood flow through the sinus. We believe the arterial flow through the cavernous sinus will be altered as a result of the changes in heart rate, systemic arterial pressure and cerebrospinal fluid pressure which we have demonstrated in our work.

When the regulatory effects of both of these physiological systems are overridden by irrigating the nasal mucosa with a medium of adequately cold temperature, on can induce selective brain hypothermia and alter the flow of cerebral arterial blood, even in man, having a single carotid artery.

Although the invention is not so limited, some of the clinical applications, as alluded to above, include selectively reducing the temperature of the brain without causing corresponding low temperatures in the remainder of the body. This has an advantage in heart surgery due to the fact that the oxygen requirement of the brain is reduced linearly with reduction in brain temperature. Therefore longer interruptions in cerebral blood flow can be tolerated. In addition, the heart can be maintained at near normal body temperature which reduces the propensity of this organ to go into fibrillation when manipulated in surgery.

Other features and advantages of the present invention will be apparent to persons skilled in the art from the following detailed description of a preferred embodiment accompanied by the attached drawing wherein identical reference numerals will refer to like parts in the various views.

THE DRAWING

FIG. 1 is a pictorial diagram of the head of a subject dog showing the irrigation of the nose and the placement of temperature sensors on the angularis oculi veins.

FIG. 2 is a graph illustrating changes in cerebrospinal fluid pressure and arterial blood pressure resulting from the irrigation; and

FIGS. 3A-3G are graphs illustrating the various vascular responses during irrigation.

DETAILED DESCRIPTION

We have shown in our laboratory that temperature alone can produce changes in the cardio-arterial system of animals which appear to vary cerebral blood flow and cerebral temperature in a manner that has not been reported elsewhere. The cardio-arterial changes are seen as a change in systemic arterial blood pressure (ABP), cerebrospinal fluid pressure (CSFP) and heart rate (HR). These cardio-arterial changes were induced by changing the temperature of the venous blood destined for the cavernous sinus by irrigating the alar fold of the maxilloturbinate. These cardio-arterial changes were such as to indicate that an increase in cerebral blood flow occurred when the temperature of the nasal mucosa was increased by irrigation with warm water, and a decrease in cerebral blood flow was indicated when the nasal mucosa was irrigated with cold water. Further, these cardio-arterial changes appear to be brought about by an automatic reflex uniquely responsive to temperature. That is, the usual response to autonomic manipulation is such as to maintain a constant cerebral blood flow; whereas the autonomic response to the temperature changes we employed appears to have altered cerebral blood flow (heat making the flow increase and cold making it decrease). Furthermore, these cardio-arterial changes have occurred independently of carbon dioxide, oxygen and pH levels of the arterial blood, as has already been reported.

We believe that brain temperature regulation is accomplished through the agency of two physiological systems. The first system provides for irrigating or circulating the surface of the nasal mucosa (more specifically, the alar fold of the maxilloturbinate) with an external media such as water, air or other gas. A portion of this temperature conditioned blood flows to the cavernous sinus where it bathes arteries which conduct blood to the brain. In our early work this system was referred to as the "external heat exchange mechanism." In our present work it is referred to as the venous temperature control system (VTCS). The second system involves control of the blood flow in the arteries just mentioned which are being bathed in the venous blood in the cavernous sinus which, in turn, has been temperature conditioned at the site of the external heat exchange mechanism. In our early work this system was referred to as the "internal heat exchange mechanism"; in our present work it referred to as the cardio-arterial control system.

VENOUS TEMPERATURE CONTROL SYSTEM

Intracerebral temperature gradients are basically dependent upon the rate of removal of heat from the brain by arterial blood. This arterial blood is cooled by
the flow of heat from the arterial blood to venous blood in the cavernous sinus. The temperature of the venous blood, in turn, is regulated by what is referred to herein as the venous temperature control system (VTCS). This system functions in two ways. The first includes a transfer of heat from the vessels in the nasal mucosa (that is, the alar fold of the maxilloturbinate) to (or from) the irrigating water or circulating air or other gas which contacts the nasal mucosa. The second manner in which the venous temperature control system works is to regulate the differential blood flow from the vessels in the nasal mucosa via the dorsal nasal veins to the angularis oculi veins on the one hand, and the facial veins on the other hand. The blood entering the angularis oculi veins flows through the ophthalmic veins to the cavernous sinus where it bathes arterial blood destined for the brain. The blood entering the facial veins by passes the cavernous sinus.

We have established through experiments the existence of a feedback control pathway from the brain to the venous temperature control system. We selected man as the experimental subject in an attempt to demonstrate this feedback control. The reasons we selected man were: (1) the anatomical arrangement of the necessary structures is similar to that in the dog; (2) the subjects would be fully cooperative and would be able to perform precise mental tasks; and (3) previous experimental work (5) has shown that mental activity increases metabolic rate which, in turn, increases heat production. As a result of our work, physiological evidence that the venous temperature control system is involved in brain temperature regulation was shown. It was found that mental activity (subtracting from 5000 by sevens as fast and accurately as possible) was accompanied by adjustments in the venous temperature control system which resulted in changes in the temperature of the angularis oculi veins (the assumption is made that an increase in metabolism in an organ is accompanied by an increase in the temperature of the organ).

Further evidence pointing to the involvement of the venous temperature control system in brain temperature regulation was seen in the unanesthetized sheep where an increase in the temperature of the reticular formation was accompanied by a cooling of the nasal mucosa. In this case an increase in the temperature changes occurring in the brain demonstrates the adjusting of the venous temperature control system to obtain optimum brain temperature.

There is also evidence that adjustments which occur in the venous temperature control systems do not depend upon conscious activity. For example, in dogs under sodium pentobarbital anesthesia, uniformity was found to be lacking in the shape of the temperature curves between the angularis oculi and facial veins on the homolateral side. These variations in temperatures indicate variations in blood flow in the respective veins, and it is therefore evident that the homolateral reflex pathways involving the venous temperature control system are functional under anesthesia. Additionally, not only are the reflex pathways between the veins on the homolateral side intact (angularis oculi and facial) but also, the reflex pathways between veins of the venous temperature control system on opposite sides are intact and functional (evidenced by lack of uniformity between the temperatures of the right and left angularis oculi veins).

These variations in blood flow between the angularis oculi and facial veins on the same side and between the angularis oculi veins on opposite sides is considered important because blood entering the angularis oculi vein enters the cavernous sinus by way of the ophthalmic vein, whereas blood entering the facial vein passes into the external maxillary and then into the external jugular vein, thus bypassing the cavernous sinus. It is evident then that the blood entering the angularis oculi vein is involved with heat transfer (consequently brain temperature regulation) between arterial blood destined for the brain and venous blood in the cavernous sinus, whereas the blood entering the facial vein is not.

We have found evidence that autonomic control exists at the level of the angularis oculi and facial veins not only in the time-response variation of these veins between cold- and hot-water irrigation as will be discussed, but also in the response of the angularis oculi veins to the clamping of the facial veins.

The mode of action of the autonomic innervation to the vessels in the venous temperature control system is considered important because of the system's involvement with brain temperature regulation, as previously mentioned. In this regard, the nasal vessels possess unique neural characteristics which indicate that their response to the autonomic stimulation is different from the responses of vessels in other parts of the body to autonomic stimulation. For example, there is reason to believe that the frequency of sympathetic impulses necessary to maintain vascular tone and to mediate reflex vasoconstriction is different in the nasal vessels than in vessels in other parts of the body. If this is the case, then the sympathetic nervous system could exert differential control over the nasal veins on the one hand and the dorsal nasal, angularis oculi, and facial veins on the other hand, by means of variation in the impulse frequency.

Another example of the uniqueness of neural characteristics of arteries and veins in the nasal passage is the beta-adrenergic receptors cannot be physiologically demonstrated in them. This means that in situations of high emotional stress, accompanied by adrenergic dominance, the only response attainable is constriction of the arteries and veins in the nasal passage, resulting in an increase in the size of the lumen of the nasal passage. This agrees with work done by others wherein adrenalin was injected intravenously and produced a marked constriction of the vessels lining the nasal passage. This constriction of the vessels lining the nasal passage. This constriction results in more cooling of the venous blood in the venous temperature control system due to an increase in the rate of heat transfer occurring from the vessels to the ambient air. This is probably due to the larger heat transfer area, and the slower rate of flow in the veins lying immediately below the mucosal surface.

If the assumption can be made that emotional stress situations are often accompanied by an increase in heat production in the brain due to an increase in mental activity, then a situation could develop during emotional stress where an increase in brain temperature would be accompanied by a decrease in the efficiency of the cooling system for the brain.

As already mentioned, we believe that brain temperature regulation is accomplished by the interaction of two systems: (1) cooling of venous blood destined for the cavernous sinus (the venous temperature control
system described previously) and (2) control of the cerebral blood flow through the cavernous sinus by a cardio-arterial control system. The more efficient the venous temperature control system is, the less the cardio-arterial control system will have to alter cerebral blood flow in order to obtain optimum brain temperature. Some of the conditions which will determine the efficiency of the venous temperature control system are: (1) environmental temperature, (2) environmental humidity, and (3) nasal respiratory rate and amplitude, and (4) emotional stress.

Cardio-arterial Control System

If the ambient temperature is excessively high, heat transfer from the nasal vessels to the inhaled ambient air is reduced and cardio-arterial adjustments occur (i.e., an increase in heart rate (HR), an increase in systemic arterial pressure (ABP), and an increase in cerebrospinal fluid pressure (CSFP)), which are evidence of an increase in cerebral blood flow. The opposite cardio-arterial adjustments occur when the temperature is excessively low. In further explanation, the venous temperature control system, by itself, is able to regulate brain temperature as long as ambient temperature remains within as yet undefined limits of hot and cold. Consequently, it is only when these limits of heat and cold are exceeded that the cardio-arterial control system comes into play by adjusting cerebral blood flow in an effort to complement the venous temperature control system. The role of the cardio-arterial control system, when the hot and cold temperature limits are exceeded, is that of obtaining optimum brain temperature regulation. These relationships have been verified by experimental work conducted in our laboratory. Using running water to obtain maximum heat transfer both toward the blood in the nasal vessels (with 42°C-50°C water irrigation) and away from the blood in the nasal vessels (with 15°C water irrigation), we were able to obtain the cardio-arterial adjustments to be described below in connection with FIG. 3.

Humidity is another factor influencing the amount of heat transfer occurring in the venous temperature control system. In this regard, humidity affects the amount of cooling which occurs on the mucosal surface. For instance, the higher the humidity, the less the heat loss occurring from the mucosal surface as a result of evaporation. For this reason, the limits of ambient heat and cold, beyond which the cardio-arterial control system comes into play to complement the venous temperature control system, are partially determined by humidity. We believe that, under normal conditions, the resultant loss of efficiency in heat transfer in the venous temperature control system due to humidity would be compensated for by the cardio-arterial adjustments pointing toward increasing blood flow as previously described.

The temperature of the blood in the venous temperature control system can be lowered by increasing the nasal respiratory rate and amplitude in man. Also, the CSFP (as part of the cardio-arterial control system) can be lowered to zero in man by increasing respiratory rate and amplitude under conditions which make it unlikely that blood gas levels would completely account for the reduction. Although different procedures were used, similar results to those in man, i.e., lowered blood temperature in the venous temperature control system during deep respiration and vice versa and lowered CSFP during deep respirations, were obtained in our laboratory using the dog. In man the temperature was lowered by increasing the respiratory rate and amplitude, whereas in the dog it was lowered by irrigation of the nasal mucosa with 15°C tap water. In both species it appears that the cold temperature limit for regulation of brain temperature by the venous temperature control system had been exceeded thereby activating the cardio-arterial control system. Also, in both species some degree of feedback control of the two systems was removed — in man by voluntary respirations and in the dog by irrigation under anesthesia. This assumption was supported by the fact that the changes in CSFP seen in both species were due to over-cooling of the venous blood in the venous temperature control system.

The interaction between the venous temperature control system and the cardio-arterial control system to obtain optimum brain temperature can be manipulated and changed in useful ways. First, as a method for inducing differential brain hypothermia, the temperature of the blood in the venous temperature control system can be lowered to a level at which not even the cardio-arterial control system can adequately compensate, and brain temperature is thereby lowered. Among the clinical benefits accruing this differential brain hypothermia are: (a) a decrease in cerebral metabolic rate allowing for extended vascular interruptions to the brain; (b) infarction can be prevented or rendered clinically undetectable when the middle cerebral artery is ligated during whole body immersion in ice water; and (c) no cellular inflammatory reaction to injury is noted, and development of cerebral edema can be suppressed as long as the brain remains cold.

Additionally, these two control systems can be manipulated so as to reduce cerebral blood flow (along with a decrease in ABP, CSFP, and HR) as noted during the cooling of the venous blood destined for the cavernous sinus. This would: (a) facilitate hemostasis during brain surgery and (b) facilitate surgical procedures by reducing brain volume and intercranial pressure.

It appears that simulating the cardio-arterial control system with temperature invokes a unique autonomic response in the circulatory system, i.e., increase in ABP (vasoconstriction) and an increase in CSFP (vasodilatation) with heat, and the opposite ABP and CSFP responses with cold. This autonomic response to temperature is unique in that it is not the all-or-nothing response usually seen with autonomic stimulation, i.e., increase in ABP (vasoconstriction) and a decrease in CSFP (vasodilatation) with epinephrine; and the opposite ABP and CSFP responses with artificial stimulation of the vagus.

In this regard, it is recognized that alpha and beta adrenergic receptors make it possible for the adrenergic nerves to dilate blood vessels as well as to constrict them. However, this dual response has not been demonstrated for the cholinergic nerves to our knowledge, consequently vasoconstriction would have to be the result of adrenergic nerve stimulation. In view of this, the constriction of cerebral vessels during cold water irrigation of the nasal mucosa (if due to autonomic stimulation) would have to be due to adrenergic action. There is definite evidence, on the other hand, that the adrenergic nerves are not responsive for the extracranial vasodilatation during cold water irrigation (decrease in ABP). That is, in our laboratory cold water
irrigation was accompanied by excessive lacrimation which is considered to be a response to cholinergic stimulation.

The all-or-nothing response of the blood vessels to stimulation of the autonomic nervous system for epinephrine (constriction) and electrical stimulation of the vagus (dilatation) appears to be for the purpose of maintaining a constant cerebral blood flow. The response of the autonomic to the stimulus of temperature applied to the carotid-arterial control system, on the other hand, appears to be for the purpose of varying blood flow (increase in ABP, HR and CSFP from heat indicating an increase in flow; decrease in ABP, HR and CSFP from cold indicating a decrease in flow).

Turning now to FIG. 1, the nature of our experiments will be described. In our early experiments, the subject was a dog, only the head of which is illustrated. Resting before the nose of the dog is a base plate generally designated by reference numeral 10 in which there are embedded an input lead 11 and a bifurcated output conduit 12 leading into the nose of the dog as illustrated. The input conduit 11 is connected to a source of cool water (not shown) or other cooled fluid such as air, and the distal ends of the bifurcated output conduit 12, 12 are located adjacent the tip of the dog's nose and oriented so as to direct a stream of the cool water principally onto the alar folds of the dog's nose. The pressure of the water passing through the output conduits 12, 12 is only sufficient to cause an upward flow of water of only a few inches.

Leading from the alar folds of the dog are two angularis oculi veins, a left and a right vein, which communicates venous blood from the alar folds into cavernous sinus of the dog. Placed adjacent the left and right angularis oculi veins are first and second thermistors designated respectively 13 and 14, and these are arranged by means of wires 16 and 17 respectively to monitor the temperature of the blood flowing in the left and right angularis oculi veins of the dog.

Experiments

Eight dogs weighing from 30–40 pounds were anesthetized and placed in ventral recumbency (as illustrated) with the head elevated by securing the zygomatic arches to a metal rack with bone screws. The long axis of the head was held at a 45° angle in relation to the long axis of the neck by ventral traction of the anterior extremity of the upper jaw.

Five dogs (Exps. 8, 9, 10, 11, 12) were anesthetized with 20 percent Urethan (ethyl carbamate manufactured by Matheson, Coleman and Bell of East Rutherford, New Jersey) in distilled water given intravenously to effect. Three dogs (Exps. 13, 14, 15) were first given Surital (sodium thiamylal manufactured by Parke, Davis & Co. of Detroit, Mich.) 4 percent intravenously. Anesthesia was taken continued with Metofane (methoxyfluran manufactured by Pitman-Moore of Indianapolis, Indiana) in a Heidbrink model 2000 closed circle anesthetic gas machine Endotracheal catheters were employed in all experiments.

Respiration was monitored only in experiments 8 through 12 by a thermistor needle probe placed in the endotracheal catheter. Body temperature was monitored via a thermistor rectal probe and a Tele-Thermometer (Yellow Springs Instrument Co., Yellow Springs, Ohio). The temperature of the right and left angularis oculi veins were monitored by needle thermistors placed on the deep face of the veins near the medial canthus of the eye as shown at 13 and 14 of FIG. 1. The temperature of the water irrigating the end of the nose was monitored by a thermistor placed in the water hose 10 at about 4 inches from the open end of the irrigating tube 12, 12 which, in turn, were placed in the nostrils as illustrated. The systemic arterial pressure was measured by connecting a fluid-filled cannula from the femoral artery to a Statham P23BC pressure transducer. The cerebrospinal fluid pressure was measured through a 19-gauge needle inserted into the cisterna magna attached by a fluid-filled cannula to a Statham P23BC pressure transducer. The EKG was also sensed and processed by a Grass Model 7P4AB Tachograph for heart rate indication. All of the transduced parameters along with a marking signal were recorded on a ten-channel Grass Model 7 ink-writing recorder. The two pressure signals and the heart rate signal were electrically damped to provide a write-out of means values.

The experimental procedure carried out with each animal was as follows. After anesthesia and attachment to the rack, a 10–15 minute rest period was allowed in order to establish resting or normal values of all recorded parameters. Then the tip of the nose (with special emphasis upon the alar fold of the manilloturbinate) was irrigated with cold water (15°C) for 10–15 minutes. The experimental trials then followed. A trial is defined as one change in irrigating water temperature (from cold to hot or from hot to cold). The hot water temperature was in the range of 45°–48°C.

After completion of the trials the brains were probed. The probe on the right side was inserted after a maximum increase in both cerebrospinal fluid pressure and systemic pressure had been observed during hot water irrigation. The probe on the left side was inserted after the right side probe had been withdrawn and after a maximum decrease in both pressures had been obtained during cold water irrigation.

A 4-inch long 25-gauge needle was employed as the brain probe. It was passed through holes 2 mm in diameter drilled through the skull with a dental burr just posterior to the frontotemporal suture and 1 cm lateral to the dorsal midline on both the right and left sides. The probe was passed ventrally through the dura mater and brain until it impinged on the bone at the base of the skull and then withdrawn a measured distance.

When the physiological aspects of the experiments were completed, the brains were removed from six dogs. Three dogs (Exps. 10, 11, 12) were removed from the rack, placed in lateral recumbency, exsanguinated, and embalmed with 10 percent formalin solution through the common carotid artery. The probetracts in the brains were then exposed and photographed. Three dogs (Exps. 13, 14, 15) were exsanguinated whole still in the rack and comparisons of the two sides of the embalmed brain were made by visual inspection and then photographed.

In all of the fifty-six reported trials during which the temperature of the irrigating water was increased or decreased, the cerebrospinal fluid pressure (CSFP) and femoral arterial blood pressure (ABP) always increased or decreased respectively. In the fifty trials in which heart (HR) was monitored, this parameter, with a few exceptions, also showed an increase or decrease with a respective increase or decrease in irrigating water temperature. The above responses when applied
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to two succeeding trials (cold to hot and back to cold) are defined by the authors to be examples of "overall normal responses." Furthermore, the temperature of the angularis oculi vein always followed in the same direction as the water temperature.

The significant results are summarized in Table 1. The table indicates that there were 32 trials carried out under Urethan-chloroaloe anesthesia and 24 with Metofane anesthesia. Also, there were 28 cold-to-hot and 28 hot-to-cold trials. The pressure and time entries in the table are the mean values obtained in each type of trial.

FIG. 2 graphically illustrates the pressure and time relationship recorded in Table 1. In FIG. 2, the abscissa is time; and the ordinate is pressure. The results of hot and cold water irrigation are shown above and below the abscissa respectively. The solid lines represent changes in cerebrospinal fluid pressure, and the dashed lines represent changes in femoral arterial blood pressure. Time was measured as starting when the water temperature change was detected by the thermistor in the water-conducting tube. The beginning point of each line, which lies on the time axis, is the mean time for the first detectable pressure change to occur. The vertical coordinate of the end point of each line is the maximum change in pressure that occurred. Finally, the horizontal coordinate of the end point of each line is the mean time it took for the maximum pressure change to appear.

FIG. 2 illustrates the following points:

Whether the irradiating water temperature was hot or cold:
1. All pressure levels reached their maximum excursions sooner under Urethan-chloroaloe anesthesia.
2. The rate of change of pressure (slope of each line) was greater in absolute value with Urethan anesthesia.
3. In 3 of the 4 pairs of lines (paired by type of pressure), the initial change in pressure came sooner when Urethan-chloroaloe anesthesia was used.
4. Greater pressure changes were noted with Metofane anesthesia.

Regardless of the type of anesthesia used:
1. All pressure levels reached their maximum excursion sooner under hot water irrigation (change from cold to hot).
2. Hot water irrigation caused greater pressure changes to occur in all cases except in the ABP measurement under Metofane anesthesia.
3. The rate of change of each pressure was greater in absolute value with hot water irrigation.

In our experiments the responses of the cardio-arterial system to temperature changes in the brain were such that the pressure and resistance relationships seen in the classical response to autonomic stimulation did not apply. That is, a decrease in both cerebrospinal fluid pressure (CSFP) and heart rate (HR) and an increase in femoral arterial blood pressure (ABP) usually seen during sympathetic stimulation; and an increase in CSFP and HR along with a decrease of ABP usually seen in vagal stimulation did not usually occur. Vasocostriction (sympathetic), vasodilatation (vagus) and changes in heart rate are manifestations, both intracranially and extracranially, of autonomic stimulation. These responses are (among other possibilities) aimed at maintaining a more or less constant cerebral blood flow. The nature of the response of the arterial system to temperature changes in our experiments, however, are interpreted to have changed cerebral blood flow. As cerebral resistance increased (vasoconstriction - decrease in CSFP), ABP did not increase, but instead it decreased. Inasmuch as heart rate (HR) also decreased, indications are that the flow of blood to the brain diminished when the alar fold of the maxilloturbinate was cooled. Further, when the temperature of the alar fold was increased by irrigation with warm water CSFP, ABP and HR increased, indicating an increased flow of blood to the brain. We therefore conclude that by cooling the nasal mucosa to a degree such that neither the venous temperature control system nor the cardio-arterial control system was able to compensate, the temperature of the brain was lowered. The lowering of the brain temperature was accompanied by cardio-arterial changes which indicated that blood flow to the brain was being reduced.

It appears that there are two routes over which the brain receives information relating to temperature changes originating at the nose. In one of the above cited reports, we noted that when the irrigating water was changed from hot to cold, the temperature response in the region of the posterior communicating artery lagged the response of the angularis oculi vein by 6 seconds. In the present series of experiments, changes in CSFP (FIG. 3c), ABP (FIG. 3b), and HR (FIG. 3a) always lagged the temperature changes in the irrigating water (FIG. 3e) and usually lagged temperature changes in the angularis oculi veins (FIG. 3f).

FIG. 3d is a common time marker for all the graphs of FIGs. 3a-3c, and 3e-3g. In one experiment, however, pressure and rate changes occurred before temperature changes were observed in the angularis oculi veins. There is a possibility in view of this that in some cases the brain is receiving stimuli by a route other than the venous return route from the nose to the cavernous sinus. The time lag between the changes in water temperature and the changes in pressures and heart rate (3-5 seconds), considering that water temperature was being measured in the conducting hose 4 inches before reaching the nose, suggests that the second route is a nerve pathway.

Body temperature varied slightly with the temperature of the irrigating water (see FIG. 3g). Increases in body temperature were presumed to be the result of warming the circulating blood by the hot water which was irrigating the end of the nose and vice-versa.

The swelling, produced by passing a probe into the brain during hot water irrigation, was found to be irreversible even after a cold water irrigation span of 10 minutes. This response appeared to be unilaterally confined to the side where the injury occurred. A rapid increase in CSFP, in addition to the increase obtained during hot water irrigation, was often seen shortly after the probe was inserted. In one such experiment the CSFP began to increase 24 seconds after insertions of the needle and during the ensuing 45 second the pressure increased by 4 mm/Hg. Since the CSFP was monitored in the cysterma magna, it is assumed that the same CSFP was exerted equally on both cerebral hemispheres. It thus appears that the swelling seen on the right side could not have been caused by interference with venous drainage from the cerebral cortex to the dural sinuses. That is, if drainage interference had been the cause both hemispheres would have been swollen. As it was, the left hemisphere actually appeared to be shrunken. The response of the brain to injury, i.e., an
increase in blood flow to the injured area, appears to be similar to the inflammatory response to injury seen in other parts of the body.

Some conception of the effect of temperature on the dynamics of the cerebral vasculature may be had when considering that CSFP was reduced from +7' to -2 mm/Hg in approximately one minute in the face of a presumed persistent swollen condition in the right cerebral cortex. However, in other trials where the probe was withdrawn, with continued hot water irrigation, the CSFP remained on the positive side.

The side of the brain probed during cold water irrigation was more firm than the side probed during hot water irrigation. This was more evident in the fresh specimens than in those that were embalmed for probe tract studies. In fact, obtaining a cross section for photography was difficult in the fresh specimens because the right side (probed during hot water irrigation) was very flacid. The left side (probed during cold water irrigation) was firm, held its shape well and sliced much the same as liver. The results obtained, relative to inflammation and swelling, by irrigating the alar fold with cold tap water are in agreement, thus far, with those of other researchers obtained by immersion of the animals in ice water.

An investigation of the relative amounts of hemorrhage in the probe tracts made during hot and cold water irrigation revealed hemorrhage to be more extensive when hot water was being used. The tract made during cold water irrigation was evidenced by a very faint gray line dorsal to the lateral ventricles.

We have concluded that there are two physiological mechanisms which are responsive to hot and cold water irrigation of the alar fold of the maxilloturbinate; namely, the venous temperature control system and cardio-arterial control system both of which have already been discussed. Three physiological variables which appear to be a manifestation of these mechanisms are systemic blood pressure (as measured in the femoral artery), cerebrospinal fluid pressure (which reflects cerebral vasodilatation or vasoconstriction) and heart rate. We have observed that these variables normally respond in such a way that they appear to vary cerebral blood flow.

a. The response of the cerebral vasculature to hot water irrigation is vasodilatation (increase in cerebrospinal fluid pressure) which is usually accompanied by a concurrent increase in femoral arterial blood pressure and heart rate.

b. The response of the cerebral vasculature to cold water irrigation is vasoconstriction (decrease in cerebrospinal fluid pressure) which is always accompanied by a concurrent decrease in femoral arterial blood pressure and usually in a decrease in heart rate.

In general, the animals had a greater sensitivity to changes in water temperature when anesthetized with urethan than with metofane. However, greater pressure changes were observed when metofane was used.

Swelling occurred when the brain was probed during continued hot water irrigation while swelling did not occur when the brain was probed during continued cold water irrigation.

The changes in vascular responses and brain temperature noted herein can be altered by varying the temperature of the skin in the area of the facial region which overlies and is drained by the dorsal nasal, angularis oculi and facial veins.

In four experiments conducted on three dogs, following endotracheal intubation, the external nares were covered with a cone and sealed to prevent air from flowing through the nasal passages. A needle thermistor (Model HTBI-HN-300, High Temperature Instruments Corp., Philadelphia, Pa.) was stereotaxically placed in the area where the internal carotid artery emerges from the cavernous sinus. Small thermisters were also placed on the deep surface of both angularis oculi and facial veins. Hot air from a commercial heat gun (Model HG 301 B, Master Appliance Corp., Racine, Wis.) was directed against the facial region overlying the angularis oculi and facial veins.

RESULTS

With each application of heat, the temperatures of the veins increased rapidly. This action was always followed by an increase in the temperature of the area surrounding the stereotaxically placed thermistor site (emergence of internal carotid artery). This latter temperature increase must also represent an increase in temperature of the areas of the brain supplied by internal carotid blood. In a representative experiment following a 2½ minute heating period, the area sensed by the stereotaxically-placed thermistor increased by 0.16°C in 4½ minutes. The temperature then fell by 0.2°C in the next 5 minutes.

Experiments on Humans

Experiments were conducted on nine separate human beings in an attempt to establish that there exists a venous temperature control system or external heat exchange mechanism at the nasal mucosa as well as a cardio-arterial control system in man. As a result of our experiments, described above in connection with dogs, we strongly believed that such a mechanism existed, but as has already been pointed out, the researchers Hayward and Baker concluded to the contrary.

In setting up these experiments thermisters were placed immediately adjacent the left and right angularis oculi veins. In some cases (represented by a single asterisk in column 3 of Table II), thermisters were placed under the skin alongside the vein. In other cases, (indicated by a double asterisk in column 3 of Table II) thermisters were placed on the skin surface directly over the vein. Hence, the temperature of the blood flowing in the angularis oculi vein through which blood returning from the nasal mucosa flows, was monitored.

It is well known that thinking produces heat in the brain. We had postulated that the brain, in regulating its own temperature would first cause a cooling of the blood returning from the nasal mucosa through the angularis oculi vein, by means of the venous temperature control system. The cooled venous blood would, in turn, cool the arterial blood flowing through the carotid artery to the Circle of Willis through countercurrent heat exchange in the cavernous sinuses (that is, the cardio-arterial control system). It is, of course, impractical to measure the temperature of arterial blood flowing to the brain or the temperature of the brain directly.

The experiment involved stimulating thinking on the part of the subjects. They were asked to subtract the number "seven" consecutively a number of times, starting with 5,000. That is, the base number from which "seven" was subtracted changes as a result of the previous subtraction. The temperatures indicated in
Table II were recorded on a polygraph recorder manufactured by Grass Instruments. Disturbances were eliminated to the extent possible from the surroundings of the subject during each experiment so as to minimize extraneous mental activity other than that which was induced by the subtraction.

During the conduction of the experiment after the temperature had leveled off, the subject would be touched or tapped, and this would indicate to him to discontinue the mental subtraction process. A thermistor was also placed alongside the arm vein to see whether there was any evidence of a more general control mechanism, and this proved to be negative, as indicated by the data in column 5 of Table II where the symbol “A” indicates the use of an arm thermistor.

Turning then to Table II, column 1 identifies the subject by number. Column 2 indicates whether the subject was left-handed or right-handed, and column 3 gives the subject’s initials, and, as mentioned, indicates whether thermistors were placed under the skin, alongside the angularis oculi vein (a single asterisk) or whether the thermistors were placed contacting the skin surface directly over the vein (two asterisks).

Column 4 gives the sex of the subject. Column 5 indicates the left (L) angularis oculi vein, the right (R) angularis oculi vein, and the median antebrachial (A) vein.

Column 6 indicates the temperature (all temperatures are in °C.) in the associated vein prior to thinking. Column 7 indicates the maximum change in temperature for the associated sensor during thinking. Column 8 indicates the net or cumulative change in temperature noted in column 7 for both left and right angularis oculi veins. Column 9 indicates the maximum change in temperature after thinking has terminated, as described above.

In columns 7–12, the arrows pointing downward indicate a decrease in temperature, and the arrows pointing upward indicate a rise in temperature.

Column 10 indicates the net or cumulative change in temperature of column 9 for both veins. Column 11 indicates the difference in temperature, in each vein, between the readings taken before and those taken after thinking.

Column 12 indicates the net change in column 11 for both veins.

For example, referring to the third subject, from column 7, it is observed that during thinking there was a maximum change of 0.5° C. in the left angularis oculi vein and 0.6° C. in the right angularis oculi vein. After thinking ceased, the temperature in these two veins rose respectively by 0.5° C. and 0.8° C.

It will be observed that for all subjects, there was a decrease in the temperature of the angularis oculi vein during thinking, and there was a corresponding increase in temperature after thinking, except in the one instance of the left angularis oculi vein of the eighth subject. This data definitely establishes a correlation between temperature change in the angularis oculi vein and the production of heat in the brain of a human being, and therefore, the existence of both a venous temperature control system and a cardio-arterial control system in the human being. By overriding this system with a cooling or heating fluid applied to the nasal mucosa, one could produce the same results in a human being as have been observed in the dog, as discussed above.

Experiments on Horses

As has already been explained, Hayward and Baker, in their research, found it necessary to classify subjects into those of the “internal carotid” and the “carotid rete” types. On the basis of their experiments, they stated that counter current heat exchange in the cavernous sinus does not occur in species with a single internal carotid artery.

Based upon the above experiment, we have found, to the contrary, that angularis oculi temperature changes in man bear a good correlation with mental activity. These experiments with man are considered to be strong evidence that external heat exchange mechanisms, similar to those found in the dog, also are present in man.

Additional experiments have been conducted on horses because of the similarity of horses to man particularly in the possession of a single internal carotid artery. Other advantages are: (1) venous drainage routes from the scalp to the ventral petrosal sinus, and (2) a venous drainage route, by way of a single vessel, from the nasal passage and the face to the cavernous sinus.

In view of work done by Layton and Sherrington (1917) on primates, a hypothesis was developed which suggested a relationship between the circulation system of the scalp and that of the nasal passage and face. It was postulated that, if the brain was concerned with regulating its own temperature independently, and the horse is similar to the primate, then cooling of the scalp would result in cooling of the blood in the ventral petrosal sinus which, in turn, would cool the internal carotid blood in the latter sinus and heating the scalp would have the opposite effect. Secondly, it was postulated that the temperature of the blood entering the cavernous sinus by way of the deep facial vein would change in the opposite direction to that in the ventral petrosal sinus. If such a system were operative, the temperature changes would offset one another, and the temperature of the blood entering the Circle of Willis would remain unchanged.

We have continuously monitored the temperature of the deep facial vein of the horse during applications of alternate heating and cooling of the scalp. The thermistors were embedded in the connective tissue outside the vessel walls, and it is therefore felt that the temperature changes in the blood were greater than those actually recorded. A plastic bag was strapped to the forehead through which cold and hot water was circulated, thereby cooling and heating the blood of the scalp. The temperature of the circulating water was kept within limits which the ponies would tolerate without showing visible signs of discomfort.

It was found, on the basis of experiments with three separate horses, that as the scalp of the horse was cooled, the temperature of the deep facial vein rose. Further, as the horse’s scalp was heated, the temperature of the deep facial vein was reduced.

Comparisons of the results obtained in the primate, horse and man, thereby point unmistakably to a functional counter current heat exchange between the single internal carotid artery and venous blood. For example, venous structure is similar in that a pathway is seen between the scalp and intracranial structures.

The direction of flow appears to be from the scalp through the skull to the intracranial area because first, the cerebral cortex is cooled and warmed very rapidly.
when cold and hot packs are applied in the primate, and secondly, the temperature response of the deep facial vein is the inverse of a temperature change when heat or cold is applied to the scalp of the horse. Further, conditions which increase intracranial temperature in man (mental activity) and in the horse (hot packs) produce similar responses in the venous pathway from the nasal and facial area of both species—i.e., decrease in the temperature of the angularis oculi in nine human subjects (Table II) and a decrease in the temperature of the facial vein in three out of three horses.

A preferred system for controlling the temperature of the fluid applied to the nasal mucosa of an animal for purposes of practicing the present invention is disclosed in the above-identified copending application, Ser. No. 171,575.

Having thus described in detail a method and apparatus for practicing our invention, persons skilled in the art will be able to modify certain of the steps disclosed and to substitute equivalent elements for those which have been described while continuing to practice the inventive principles; and it is, therefore, intended that all such modifications and substitutions be covered as they are embraced within the spirit and scope of the appended claims.

We claim:

1. A method of treating animals comprising: selecting an animal from the class consisting those mammals having a single internal carotid artery carrying blood to the brain; and locally irrigating the region of the face or nasal passage drained by the angularis oculi and other facial veins with a fluid at a predetermined temperature sufficiently different from the normal body temperature of said mammal to override the venous temperature control system and thereby control the flow of blood to the brain of said animal.

2. The method of claim 1 wherein said step comprises contacting the nasal mucosa of said animal with said fluid.

3. The method of claim 1 wherein said step comprises continuously contacting said region locally only with a gas of controlled temperature and humidity, the temperature of said gas being different than the temperature of the ambient atmosphere surrounding said animal.

4. The method of claim 1 wherein said step if irrigating comprises directing a stream of cooled fluid against the alar fold of the maxilloturbinate of said animal.

5. The method of claim 1 wherein said fluid is cooled beneath the normal body temperature of said animal to thereby induce selective brain hypothermia in said animal.

6. A method of treating animals comprising: selecting an animal from the class consisting those mammals having a single internal carotid artery carrying blood to the brain; and locally irrigating the region of the face or nasal passage drained by the angularis oculi and other facial veins with a fluid cooled to a predetermined temperature sufficiently below the normal body temperature of said mammal to override the venous temperature control system and thereby decrease the cerebrospinal fluid pressure, the femoral arterial blood pressure and the heart rate of said animal.

7. The method of claim 6 wherein said step comprises contacting the nasal mucosa of said animal with said fluid.

8. The method of claim 6 wherein said step comprises continuously flushing the facial skin in said region with a gas having a controlled temperature and humidity, the temperature of said gas being different than the temperature of the ambient environment surrounding said animal.

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