An Experimental Study of Cerebral Blood Flow in Hypertension

By

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In hypertension, disturbance in cerebral blood flow which used to occur in this disease can be considered one of the most important factors for its clinical symptoms, moreover some presumption can be expected also of the genesis of cerebral hemorrhage by investigating the disturbed brain circulation; namely a lot of cerebral symptoms, such as insomnia, headache, tinnitus, vertigo, reduced power of concentration, failing in memory, mental irritability, etc. are attributed usually to the congestion or deficiency of oxygen supply in brain. It has been pointed out by a series of investigators such as Roy and Sherrington,1) Kawaguchi,2) Yama-kita and others, that in case of raised blood pressure the blood flow in the brain undergoes to some alternation, while Williams3) and Kety and co-workers4) will deny this fact.

In order to give some contribution to this problem which is not yet settled, the present experimental investigation has been undertaken, measuring the cerebral blood flow of the rabbits in the earlier and later stage of hypertension which was induced in them experimentally by the method of Goldblatt.5)

EXPERIMENTAL

Method

Rabbits weighing about 2.5 kg. were employed, those which show extraordinarily variable blood pressure levels in healthy condition being excluded. In them the renal ischemia of desired degree was induced by means of Goldblatt's method, a specially devised artery silver clamp, with a graduated acting screw and compressing plate being applied to the main renal artery, so that the grade of arterial constriction could be varied and controlled to the desired degree. The blood pressure was measured in ear of rabbit frequently for a long while during the course of experiments
by using conservative method of Kuraya. This original method was modified, the central auricle artery in its most dilated condition being brought at a definite point peripheral of the tambour and the pressure acted upon when the blood flow has begun again to pass through that point with pulsation being read; the readings thus obtained were nearly the same with those obtained by the method of Kawaguchi. The fluctuation of blood pressure could be also measured sensitively.

There are devised various methods for the determination of cerebral blood flow in animals. Yamakita, perceiving that the superficial temporal vein in rabbit communicates with transversal sinus through temporal emissarium and pours its venous blood into the external jugular vein, determined the cerebral blood flow by measuring the outflow of venous blood from the cannula inserted in the superficial temporal vein after tying the other branches which do not communicate to the temporal emissarium. In the present experiments Yamakita’s method was employed, thereby also the oxygen content of the blood samples thus obtained from the superficial temporal vein was compared with that of arterial blood from femoral artery. For the determination of the oxygen content of the blood Barcroft’s differential blood gas apparatus was used. The values obtained by Fleischl-Miescher’s hemoglobinometer were applied as the criteria determining the blood concentration.

In a series of experiments the carotid gland and neighbouring nervous plexus around carotid sinus in an extent of 10 mm. on both sides were extirpated, in order to observe the influence of the carotid sinus upon the cerebral blood flow in hypertensive animals. In a small group of rabbits with hypertension the findings of ocular fundus were observed by means of electrical ophthalmoscope.

Results

I. Control experiments on normal rabbits (Table I).

**Table I**

Mean Values in Normal and Hypertensive Rabbits

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure mm Hg</th>
<th>Oxygen content Vol. %</th>
<th>Oxygen consumption $O_2$</th>
<th>Oxygen consumption rate %</th>
<th>Venous blood flow (v) c.c.</th>
<th>$\Delta O_b/V$</th>
<th>$\Delta O_s/V$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>76.2</td>
<td>18.05</td>
<td>11.50</td>
<td>6.55 (1.27)</td>
<td>36.4 (7.16)</td>
<td>2.5 (0.73)</td>
<td>2.94 16.51</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>106.0</td>
<td>18.03</td>
<td>13.40</td>
<td>4.63 (1.97)</td>
<td>25.7 (8.08)</td>
<td>2.91 (1.31)</td>
<td>1.96 13.47</td>
</tr>
<tr>
<td>Changes in %</td>
<td>+39.6</td>
<td>0</td>
<td>+16.50</td>
<td>-29.3 (16.50)</td>
<td>-32.9 (-33.3)</td>
<td>+16.4 (-33.3)</td>
<td>-19.8</td>
</tr>
</tbody>
</table>

The figures in parenthesis express unbiased disperse.
Of 17 rabbits, 9 were experimented on one side of the superficial temporal vein and 8 rabbits on its both sides at interval varying 2 to 5 days. The measurements yielded following data: The mean value of the oxygen consumption ($\Delta O_2$) is 6.55 (vol %), its unbiased disperse 1.27. The oxygen consumption rate ($\Delta O_2/AO_2$) on an average 36.4%, its unbiased disperse 7.16. The amount of the venous blood flow from the superficial temporal vein per minute ($v$) is in the mean 2.5 cc., its unbiased disperse being 0.73. The quotient of oxygen consumption by the venous blood flow is on an average 2.94. The mean value of the product of oxygen consumption and the venous blood flow 16.51.

II. Experiment on hypertensive rabbits. (Table I)

In 16 rabbits the artery clamp was applied to the main renal artery on one or both sides in order to induce arterial hypertension by renal ischemia. In the first series of the experiment (9 rabbits), in which the changes in the earlier stage of hypertension were to observe, the artery clamp yielding about 1 mm. calibre to the renal artery was applied only on one side. In the majority of the cases apparent rise in the blood pressure appeared in one or two days after operation and continued for about one week, afterward used to discontinue. In one case its duration was longer than 10 days. In another one case the animal died shortly after the rise of blood pressure and in 2 cases there could be no significant change in blood pressure observed.

The ischemic kidney showed atrophy or cloud swelling and in the majority ischemic infarcts of irregular form in the cortical area where microscopically severe parenchymatous degeneration or necrosis could be seen. No change in the control kidney. Weight of kidneys on an average: 9.1 g. on ischemic side, 10.7 g. on control side.

In the second series of the experiments which numbered 7, the changes in the later stage of hypertension were investigated. The experimental constriction of the main renal artery was carried out on both sides, one after another in two sittings with the interval varying from 1 to 7 days. On the first side the calibre of the artery was allowed about $\frac{2}{3}$ mm., on the second side about $\frac{1}{2}$ mm.

The elevation of the blood pressure occurred in one or two days after the first constriction and continued in general more than 3 weeks, though in a few cases it showed temporarily a slight fall immediately after the second arterial constriction on the other side. In 2 cases the animal died in 2 weeks and in 3 within a few days after the first constriction with sudden rise of blood pressure. In on case the blood pressure remained in normal level.

In kidneys of those animals with 2 exceptions the atrophy was more significant on the side in which the clamp had been applied at first than
on the another side. In 2 cases, in which the increased blood pressure maintained the high level for more than 25 days, the kidney of the first side showed resp. 3.2 g. and 2.5 g. in weight and the parenchyma was almost replaced by connective tissues. The mean weight of the kidneys with the first cramping was 10.06 g. and that of those with the second cramping 11.5 g.

The data obtained by the measurement fluctuated in a wide range as it was in control experiments. The rise of blood pressure after constriction of the main renal artery was on an average 39.6%, the mean increase of the pulse rate was 6.1%, that of respiration rate 16.1%. Those changes in the pulse and respiration rate were significant in the initial stage of hypertension and lessened later.

Oxygen consumption ($\Delta O_2$) in the brain and its rate ($\Delta O_2/\Delta O_2$):

The difference between the arterial and venous oxygen contents, that is, the oxygen consumption in the brain was 4.63 (vol %) on an average. This value is 29.3% less compared with that in control experiments. Its unbiased disperse is 1.97. The calculated oxygen consumption rate is 25.7, thus being 32.9% less than that in control experiments; the unbiased disperse is 8.08.

The venous blood flow from superficial temporal vein:

This was in the mean 2.91 c.c. per minute, which is 16.4% more than that in control experiments; the unbiased disperse is 1.32.

Quotient of oxygen consumption by venous blood flow:

1.96 on an average, which is 33.3% less than that in control experiments.

Product of oxygen consumption and venous blood flow:

The average value is 13.47 and 19.8% less than that in control experiments.

The changes above mentioned were more significant in the initial stage (within 3 days after the arterial constriction) than those in the later stage of hypertension (Table II). The same is also true in those experiments in which the renal ischemia was caused on one and the same rabbit twice one side after another in a certain interval (Figg. 1 and 2), the difference of the data between two stages being much greater, compared with those obtained in two similar stages in one and the same normal rabbit.

The difference of blood concentration between the venous blood flowing out from the brain and the arterial blood:

In normal rabbits, the difference of blood concentration observed by the hemoglobin value between the superficial temporal vein and femoral artery is very slight. The mean value of 5 cases is 0.2%, while this value amounts in rabbits with hypertension to 5.9% on an average of 20 experiments. This tendency is more apparent in the early stage of hypertension, namely 7.63%, and lessens later, the mean value being reduced to 3.74%. 
TABLE II
Mean Values Obtained in 2 Stages of Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure mm Hg</th>
<th>Oxygen content Vol %</th>
<th>Oxygen consumption ΔO₂</th>
<th>Oxygen consumption rate %</th>
<th>Venous blood flow (v) c.c.</th>
<th>ΔO₂/V</th>
<th>ΔO₂V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earlier stage</td>
<td>102</td>
<td>17.96</td>
<td>4.00</td>
<td>22.3</td>
<td>3.3</td>
<td>1.36</td>
<td>13.20</td>
</tr>
<tr>
<td>Later stage</td>
<td>108</td>
<td>18.28</td>
<td>5.49</td>
<td>30.1</td>
<td>2.6</td>
<td>2.37</td>
<td>14.22</td>
</tr>
</tbody>
</table>

Fig. 1. Cerebral blood flow in two stages of hypertension.

The results may be summarized as follows:
1. The oxygen consumption and oxygen consumption rate in the brain diminish remarkably after renal ischemia, but later recover nearly to the normal level.
2. The venous blood flow from the brain increases apparently after renal ischemia, diminishes later approaching to the normal value.
3. Accompanied by those changes, ΔO₂/V and ΔO₂V within three days after onset of hypertension are significantly less than those in normal animals, afterwards increasing and approaching to the normal level.

The influence of extirpation of carotid sinus upon the changes of cerebral blood flow in hypertensive rabbits

In order to observe whether carotid sinus acts or not any influence
Fig. 2. Oxygen consumption rate in the brain in two stages of hypertension.

upon the changes of cerebral blood flow of hypertensive animals, in 4 rabbits the extirpation of carotid sinus on both sides were performed. The extirpation was carried out in the later stage of the hypertension when the changes of cerebral blood flow should be minimized and after short interval the cerebral blood flow was measured (Table III). After the extirpation the blood pressure used to rise temporarily moreover. In all those animals definite changes could be seen: namely, decrease in oxygen consumption and oxygen consumption rate, increase in blood flow became remarkable again. Those changes are nearly similar to the values observed in early phase of the hypertension.

Findings in ocular fundus

In 7 rabbits with experimential hypertension caused by Goldblatt's method, findings in ocular fundus before and after elevation of blood pressure were examined. With sudden rise of blood pressures tortuosity and fullness of central arteries of retina could be noticed almost in every case; in 3 cases they were particularly significant. These findings dimi-
nished after 10 to 11 days, arteries themselves also became narrower successively. In all cases in which the examination of the ocular fundus was carried out for 14 days no other findings as seen in clinical cases of hypertension could be confirmed; in some cases slight dilation of central retinal vein was noticed, but this tendency was not significant in general.

**DISCUSSION**

Since the experimental hypertension due to renin has been ascertained by Goldblatt,9) Page10-13) and their co-workers the pathologic physiology of hypertension has caused much interest of investigators, and it seemed once presumable that not only the question on the genesis of renal hypertension but also that of essential hypertension could easily be solved. But this is in fact not the case, the problem of hypertension remaining yet entirely undermined, though it is out of doubt that the acting point of the pressor substance lies in the wall of small vessels or capillaries which undergoes to contraction or increase of tension.

The present experiment performed on rabbits with Goldblatt’s hypertension has revealed that the blood flow in the superficial temporal vein seems apparently, though not considerably, is augmented, a fact which indicates accordingly some increase of blood flow in the brain.

Arguments have been repeated on the reaction of cerebral vessels to adrenalin; the majority of investigators, even those who assert contraction of cerebral vessels by this drug accept at least transient increase of cerebral blood flow with onset of general arterial hypertension by adrenalin.14-17) In rabbits with Goldblatt’s hypertension also the small blood vessels in brain which are provided with only scanty smooth muscles and vasoconstrictor nerves, will dilate to some extent passively with sudden increase of arterial blood pressure. But its duration is too long compared

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**Table III**

<table>
<thead>
<tr>
<th>No. of exp.</th>
<th>Experiment before extirpation</th>
<th>Experiment after extirpation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood pressure mm Hg</td>
<td>Oxygen consumption rate %</td>
</tr>
<tr>
<td>24</td>
<td>120</td>
<td>31.2</td>
</tr>
<tr>
<td>26</td>
<td>100</td>
<td>29.2</td>
</tr>
<tr>
<td>27</td>
<td>100</td>
<td>25.3</td>
</tr>
<tr>
<td>28</td>
<td>90</td>
<td>31.1</td>
</tr>
<tr>
<td>Mean</td>
<td>90</td>
<td>29.2</td>
</tr>
</tbody>
</table>
with the case of adrenalin hypertension; there should be necessarily performed more advanced researches on other agents which could create disorder on blood circulation in the brain.

On the other hand, the oxygen consumption in the brain of hypertensive rabbits diminishes remarkably even if the increase of hemoglobin concentration (or decrease of blood water) in a unit volume of the blood samples be taken into consideration. Naturally, the amount of gaseous interchange between blood and tissues depends on the extent of area of capillaries, namely their surface, where it takes place, and on the oxygen demand of tissues; especially it is modified by the velocity of blood flow in capillaries. When the blood flow in capillary increases while the oxygen consumption of the tissues remains unchanged, the used oxygen amount in a unit volume of blood should be lessened consequently. In those cases, the fact that even $\Delta O_2 V$, that is the oxygen quantity transferred into the brain tissue in every minute is decreased, indicates that owing to the increased cerebral circulation there is not time enough for the interchange of gases between blood and brain tissues. The characteristic structure of brain capillaries, as confirmed by Sepp\textsuperscript{18} may be turned to account for the explanation of the fact above mentioned, as good as for the augmented concentration of venous blood flowing out from the brain; with onset of hypertension, the precapillaries and the postcapillaries may be dilated passively, while the capillaries in the narrow sense will remain without remarkable change in their calibre. It is readily presumed that through the dilated precapillary the blood water goes out in an increased amount into the tissue, while the postcapillaries which are also dilated, cannot take up enough tissue fluid into the blood stream. This may have some connection with the increased amount of cerebrospinal fluid in experimental hypertension, a fact recognized by Kawaguchi.\textsuperscript{29} As a result of the dilatation of pre- and postcapillary area, the velocity of blood flow in the capillaries in the narrow sense will be accelerated and the blood pressure in them should be relatively decreased in accordance with the hydrodynamic law of continuity, thus leading to diminished oxygen discharge.

In the present experiment it has been pointed out that the above mentioned changes in cerebral blood flow are more significant in the early stage of the experimental hypertension, and minimized gradually in the later stage. And as this latter phenomenon can occur without any lowering of the blood pressure, it may be presumed that some new changes must take place in the cerebral blood flow. It is generally acknowledged by excellent works of Hering\textsuperscript{19} and Heymans\textsuperscript{20} that the blood flow in brain is controlled by carotid sinus. Our experiment revealed that after denervation of the carotid loop the changes in cerebral blood flow became significant again instead of approaching to normal level. Indeed, there
may happen in the course of time contraction of cerebral arterioles over-
coming the increase of blood pressure; but those facts above stated support
the presumption that the carotid sinus displays an action though scanty,
gradually to bring the cerebral blood flow in normal condition.

Unevenness and tortuosity of retinal artery which were observed
frequently in present investigation in the course of elevation of the blood
pressure, have been pointed out also by Goldblatt, Kinukawa, Kuwa-
jima and others. Those findings appeared in accordance with the
change in the cerebral blood flow, which are regulated step by step by
carotid sinus or by arterioles themselves.

Thus, it is ascertained that there are at least two phases in the change
of cerebral blood flow in arterial hypertension, and it can be easily under-
stood that there exist certain differences between experimental hyper-
tension induced rapidly and the clinical hypertension, which comes about
gradually under the compensatory action of blood pressure regulating
system including carotid sinus.

The experimental data obtained in the present investigation cannot
simply be applied for understanding the pathologic physiology of the
arterial hypertension in human body, where the regulation of blood supply
to the brain by carotid sinus and others is much predominant in comparison
with that of rabbits. Nevertheless, considering that in some patients with
hypertension, the oxygen consumption in the blood circulating through
the brain is lowered slightly as has been pointed out by Williams, it cannot
be neglected the possibility, that there may occur similar procedure in
human body too, especially in cases of hypertension with certain disturbance
in blood pressure regulating system such as carotid sinus function, as was
proved in arteriosclerosis, when sudden onset of high blood pressure attacks
the circulation in the brain.

Unexpected seizures of cerebral hemorrhage accompanied by sudden
rise of blood pressure in cases where apparent arterial hypertension could
not be proved in the clinical history, which has been reported by Michi-
suga and many other investigators, should be of interest when we con-
sider its mechanism basing on the presumption deduced from the experi-
mental data as above stated; rapid onset of hypertension followed by
dilatation of cerebral blood vessels and increase of blood flow in the brain
may bring about cerebral hemorrhage in some cases.

Conclusions

1. In rabbits with experimental hypertension caused by Goldblatt's
method, especially in case of its rapid onset, the cerebral blood flow is in-
creased and the oxygen consumption in the brain is lowered; judging by
the hemoglobin content, the venous blood flowing out of the brain is con-
centrated to some extent. It may be presumed that those changes may depend partly upon the dilatation in the pre- and postcapillaries, what Sepp calls. The findings in optic fundi support this presumption.

2. These changes are more significant in the early stage of experimental hypertension and gradually minimized in the course of time. Control by carotid sinus in this procedure seems significant.

3. These findings may suggest the changes in cerebral blood flow in arterial hypertension rapidly occurring in human body, as well as the mechanism of cerebral hemorrhage in some clinical cases.

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