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Influence of blood viscosity on cochlear action potentials and oxygenation

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Impairment of the cochlear blood supply of guinea pigs was induced in order to study the effects of hypoxia on the cochlear action potentials. The oxygenation of the cochlear structures was decreased by perfusing the ears with polycythemic hyperviscous blood. The validity of using this model of cochlear blood flow was based on the propensity of the blood to flow in a laminar way. Because of the streamlined flow pattern, the blood supplied by the two vertebral arteries does not mix within the common trunk of the basilar artery. The retrograde injection of polycythemic hyperviscous blood into one vertebral artery will affect the ear on the injected side only. The high viscosity of the polycythemic blood decreases the rate of flow of blood through the cochlear vessels; the high oxygen content of this blood, however, avoids hypoxia of the cochlea. Therefore, in order to make the slowdown in the blood flow evident, its oxygen content was reduced to a 'precritical level' before it was infused. Injecting normoviscous blood with a 'precritical level' of oxygen caused a mild reduction in the scala media pO_2 of 15.2% for the whole group of twenty animals. The hyperviscous blood with the same level of oxygenation, however, reduced the pO_2 in the scala media to 53.3% of normal. These findings explain the difference in the altered click-evoked action potentials in the two groups of animals.

Key words: blood-hyperviscosity; hearing loss; cochlear action potential; cochlear oxygen tension.

Introduction

In the last two decades, considerable attention has been paid in the literature to the problem of increased blood viscosity. During this period, the influence of the viscosity of the blood on the microcirculation in different systems of the body was analyzed in remarkable clinical and experimental studies.

Dintenfass [4–7] concluded that, in patients with coronary heart disease or myocardial infarction, an increase in viscosity of the blood could be due to any of several factors, including increased hematocrit, aggregation of erythrocytes, and/or rouleaux formation. Even when each of these factors deviates only to a limited extent from the normal, the sum of the small deviations contributes to the magnitude of the pathology. Dintenfass stressed that physicians must look for these small deviations, which are generally present a long time before any dramatic events occur.

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The same conclusion was reached by other authors as well [1,2,26].

The dangerous effects of increased blood viscosity have been investigated as they are in other body systems [8,11], especially as they are noted in conjunction with brain dysfunction. However, the correlation between hyperviscosity of the blood and a deficit observed clinically or experimentally is not simple: too many factors may cause decreased blood perfusion. For example, in a study of the effects of blood viscosity on the medullary and cortical blood flow in the kidneys of dogs [18], medullary blood flow was found to be viscosity dependent while cortical flow was unaffected by an increase in blood viscosity.

As far as the inner ear is concerned, there is clinical and experimental evidence that cochlear impairment could be the result of hyperviscosity of the blood. Davis and Nilo [3] described the noxious effects of polycythemia vera on hearing and the beneficial results obtained by periodic phlebotomy. By reducing the red cell concentration and hence the viscosity of the blood, the labyrinthine perfusion improved, and the hearing with it. The beneficial effects [23] of pharmacologically lowering blood viscosity in patients with sensorineural hearing loss have also been reported [27]. It was concluded that the slow progressive deterioration of hearing which accompanies sickle cell disease in Jamaicans is the result of the sickling and sludging of red cells in the cochlear venous system.

A common limitation of the techniques used for studying the influence of blood hyperviscosity on hearing was that the impairment in the microcirculation was in general affecting the whole body. Thus, not only the normal functioning of the ear was affected, but functions of many vital systems of the body were also impaired. Under such conditions the changes induced in the cochlea were aggravated and/or obscured by the deterioration of the animals' general condition. To avoid these limitations, in this study an effort was made to interfere with the regional blood flow from which the ear receives its supply, the slowdown of the cochlear blood flow being obtained by increasing the viscosity of the regional blood.

McDonald [17] had shown that blood streaming from the two vertebral arteries into the common trunk of the basilar artery forms two separate columns. Due to the laminar flow pattern of the blood in the basilar artery, these two columns flow side by side without mixing, each one supplying exclusively the vessels emerging from the same side of the basilar artery. The two columns of blood remain separate even when blood is injected in retrograde fashion at a set flow rate through the auxillary arteries [19].

Based on McDonald's observations, we constructed an experimental model using guinea pigs. The right ear of each guinea pig was supplied with blood having normal hematocrit and oxygenation, and the left was supplied with blood having high hematocrit and high viscosity with reduced oxygen-carrying capacity. The oxygen content of the high-viscosity blood was reduced because polycythemic blood in particular may have higher concentrations of oxygen than are necessary for effective tissue perfusion, and if the slowdown in the blood flow caused by the high red cell concentration is not too severe, tissue oxygenation is not impaired. In fact, normal tissue oxygenation can be ensured when the pO_2 in the inspired air is decreased, as it is at high altitudes, by an increase in the hematocrit. Even blood normally circulated

to the ear has higher oxygen content than necessary for tissue perfusion. Previous studies found [12] that the oxyhemaglobin in the blood of cats in which hypoxia had been induced had to be reduced to 30% in order to observe a decrease in the amplitude of cochlear microphonics corresponding to a 5 dB decrease in stimulus intensity. Gafni and Sohmer [10] noted that a pO_2 of 40–60 mmHg for arterial blood was associated with a reduction in the endocochlear potential.

In a previous study [20] it was shown that normal cochlear action potentials (AP) could still be recorded when the blood perfusing the cochlea had a normal hematocrit but a pO_2 of only 30 mmHg if the blood supply to the ear remained normal. This level of oxygen tension was termed the 'precritical level'. In the present study it was decided first to perfuse the left cochlea of guinea pigs with blood having a normal hematocrit and a pO_2 of 30 mmHg, and then to perfuse the same cochleas with hyperviscous blood (hematocrit 75%) and the same pO_2 of 30 mmHg. The hypoxic effect of hyperviscous blood was determined by measurement of cochlear action potentials and the scala media pO_2 measurements.

Materials and Methods

In guinea pigs weighing 500 g each an electrode for recording action potentials (AP) was implanted in the left facial canal using a technique already described [13]. The acoustic stimulus consisted of clicks with alternated polarity induced by electrical square waves of 60 μs duration and repetition rate of 10/s. The train of acoustic clicks generated in this way started with a condensation, followed by a rarefaction phase. Averaging a certain number of cochlear responses to such stimuli eliminated the cochlear microphonics because the latter are phase dependent while APs are unaffected by averaging.

The stimulus was delivered in a sound field, and the intensity was measured at the position of the animal's head. An Amplaid ERA Mk III was used to generate sound in this study, this being a two-channel function generator which triggers a Medelec electrophysiological system. This system includes a biological amplifier with mobile preamplifier, filters for band-width selectivity, an averager and a four-channel oscilloscope with three modes of display. Permanent recordings of the cochlear averaged responses were made on photosensitive paper by a fiber-optic system incorporated in the Medelec equipment.

The cochlear AP recorded by this experimental setup is a biphasic, double-peaked response, as can be seen at the top of Fig. 1. The first negative deflection is labeled N_1 and the second is labeled N_2. Each tracing is the averaged response to 32 presentations.

The magnitude of the AP was evaluated by measuring the distance between the peak of the first negative deflection and the peak of the following positive deflection. By knowing the deflection given by the calibrating voltage one can express in microvolts the magnitude of the recorded AP.

By plotting the amplitude of the AP in μV against the click intensity in dB at increasing sound pressure levels, an AP input–output curve was obtained.

The minimal click intensity which induces a detectable and repeatable deflection of the baseline was considered to be the 'visible threshold'.

Blood to be injected was prepared shortly before the experiment by cardiac puncture from the other guinea pigs. A portion of the collected blood (the quantity required for injection) was reconstituted so that the hematocrit was 75%. The viscosity of the reconstituted blood was measured at eight shear rates using the Wells–Brookfield microviscometer. The mean measured values ranged between 7.8 centipoise (cp) for a shear rate of 230 s^{-1} up to 110.46 cp for a shear rate of 1.15 s^{-1} (see Fig. 2 and Table I). The mean viscosity of the eight measured shear rates was 42.87 cp. The pO_2 of the blood was reduced exactly to 30 mmHg by the tonometric method.

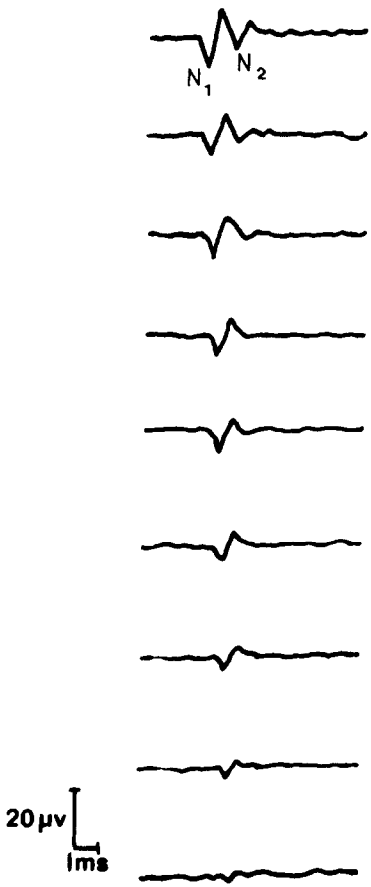

Fig. 1. AP response to clicks at 85 dB SPL. Each tracing represents the average of 32 click presentations. During the infusion with hyperviscous blood and limited pO_2 the averaged AP responses were continuously obtained, while the intensity of the stimulus remained constant. The figure shows, from top to bottom, progressive decrease in AP amplitude caused by induced cochlear hypoxia.

TABLE I

VISCOSITY (cp) OF RECONSTITUTED BLOOD OF GUINEA PIGS AT 40% AND 75% HEMATOCRIT (Hct)

Shear rate (s^{-1}):	1.15	2.30	5.75	11.50	23	46	115	230	Mean of 8 shear rates
40% Hct	17.46	14.26	8.97	7.12	5.52	4.74	3.8	3.44	6.96
75% Hct	110.46	82.7	56.3	37.5	23.3	14	10.9	7.8	42.87

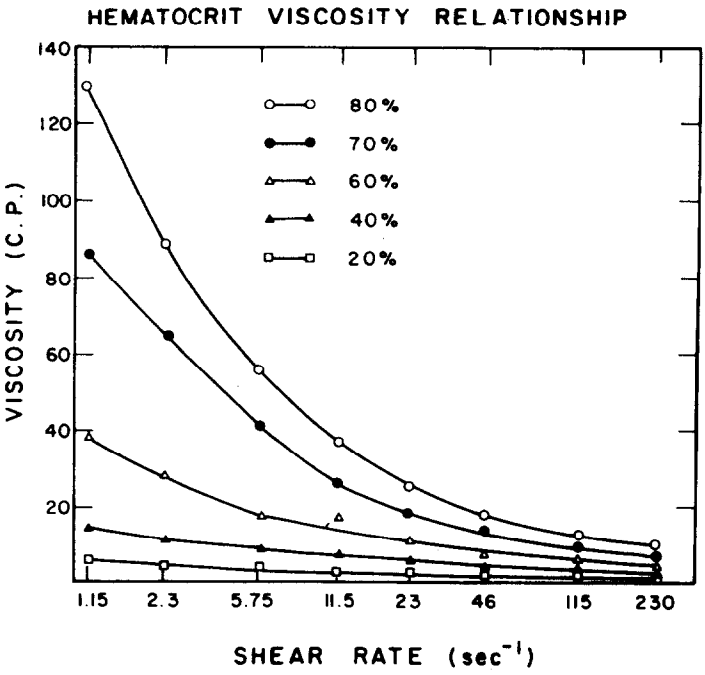

Fig. 2. Mean viscosity of reconstituted blood of Hartley guinea pigs at different hematocrit levels, established in our laboratory.

Regional intra-arterial blood infusion

The guinea pigs were sedated with Nembutal, 2.5 mg per 100 g body weight injected intraperitoneally, and local anesthesia was produced. The two axillary arteries were then cannulated. The electrodes were connected to the Medelec electrophysiological system. A whole input–output function was obtained to be used as the normal reference.

The procedure for the intra-arterial infusion was as follows: The cannula from the animal's right axillary artery was connected to the syringe containing oxygenated blood with normal hematocrit and normal viscosity, and the left cannula was connected to the syringe with high-hematocrit, high-viscosity blood. The syringes were mounted on an infusion pump (syringe pump Model 355, SAGE Instruments) and connected via a T-tube from the right cannula to a Statham pressure transducer (model P37). The infusion was set at a constant flow rate of 1 ml/min.

For the first 10 experiments, in the first stage, 4 ml of blood having a pO_2 level of 30 mmHg but normal hematocrit were injected. The normal measured viscosity of the normal blood was 3.44 cp at a shear rate of 230 s^{-1} and 17.46 cp at 1.15 s^{-1}. The mean normal blood viscosity of the eight measured shear rates was 6.96 cp. If no change in the cochlear action potential was observed, 4–5 ml of blood were withdrawn from the right cannula to avoid significant increase in the animal's total blood volume. Then, in the second stage, the continuous infusion was changed to

hyperviscous blood with pO_2 of 30 mmHg, which was infused for an additional four minutes. No changes in the cochlear AP were induced by the blood having normal hematocrit and pO_2 of 30 mmHg, as was expected from the results of a previous study [20]. In the remaining 20 experiments only the high-hematocrit, high-viscosity blood was injected.

Measurement of pO_2 in scala media

The pO_2 in the scala media was measured using the polarographic method and platinum–glass micro-electrodes. The procedure necessitates immobilization of the animal. Therefore, the guinea pigs in this group were anesthetized with diallylbarbituric acid and urethane, 0.08/100 g body weight, tracheotomised and artifically ventilated. During the experiment, the animals were kept warm by heating pads. Pulse rate and blood pressure were continuously monitored.

Cannulating the axillary arteries, preparation of blood for infusion, and the infusion itself were done in essentially the same ways as in the experiments to measure AP. For polarographic equipment, we used a Transidyne General (Ann Arbor, Mich.) Chemical Micro Sensor with microelectrodes made by Frederick Haer Co. (Brunswick, Maine) model 30-10-3. A silver–silver chloride wire placed in the neck muscle was used as a reference electrode. Every microelectrode was calibrated before and after the experiment. Sometimes significant differences were observed and the results obtained in this experiment were discarded. With the help of a micromanipulator the electrode was introduced into the scala media through the pars pectinata of the basilar membrane, as described by Lawrence and Nuttal [16].

Results

Cochlear action potentials

The labyrinthine hypoxia induced by perfusing the ear with high-viscosity blood caused three kinds of changes in the cochlear response to sound: (1) rise in threshold; (2) fluctuating AP response; (3) changes in the slope of the input–output curve. Each parameter was analyzed by paired t-test, comparing pre- to post-infusion state.

As has already been mentioned, the 10 guinea pigs that were first infused with normal-hematocrit blood and then were infused with high-hematocrit, high-viscosity blood showed no change in AP after the infusion of the normal-hematocrit blood. However, while infusing or immediately after infusion of hyperviscous blood a rise in threshold was observed in 17 out of the whole group of 30 animals (56.6%).

A final control measurement of the amount of threshold shift was made after the experiment by comparing the input–output curve obtained before and after the blood infusion. The statistically significant threshold shift observed in this group of 30 animals ranged between 5 and 30 dB, with a mean value of 9.16 dB for the whole group ($t = 5.25$, $P < 0.001$) (Fig. 1).

Fluctuating AP response

The first, and sometimes the only, sign of cochlear impairment was a change in

the magnitude of the AP response to clicks. It appeared while the high-viscosity blood was being infused, or immediately afterward, and disappeared when the normal blood supply returned to the ear. This fluctuation was observed at the intensity of 15 dB above the threshold because the monitoring of the AP during infusion was done at this intensity (Fig. 3).

To evaluate this phenomenon, the difference in μV between the maximum and minimum amplitude of AP response at this click intensity before infusion was calculated and compared with the maximum and minimum amplitudes measured while the hyperviscous blood was being infused. By this method, it was found that in 10 out of 30 animals which received hyperviscous blood a significant fluctuation in the AP response occurred during infusion ($t = -3.91$, $P < 0.001$). Of the 10 guinea pigs which received normal blood, in only one was any fluctuation of AP response observed.

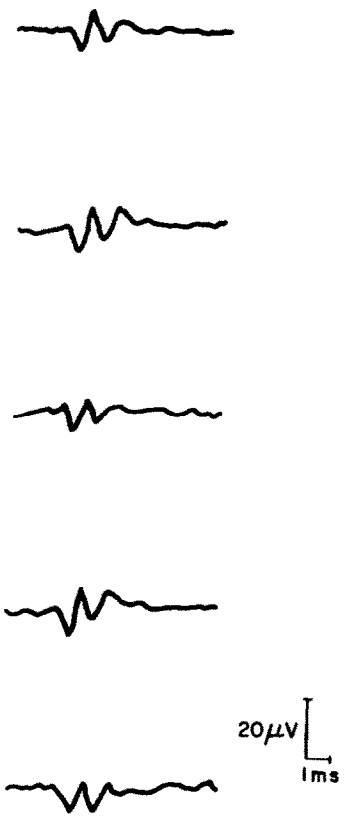

Fig. 3. Fluctuating AP response to clicks at 65 dB SPL. Each tracing represents the averaged response to 32 click presentations. During infusion with hyperviscous blood, the AP responses were continuously recorded. A section of the response record taken at the beginning of the induced cochlear hypoxia is shown. From top to bottom: a sudden decrease in amplitude in the third recording with return to normal in the fourth and again decrease in the fifth recording. The five tracings were made over a total of 1.5 min.

Changes in the slope of the input–output curve

An examination of the literature showed that no generally accepted method of evaluating the slope parameter has yet been presented. In this study the change in slope occurred mainly in cases with shift in threshold and normal or near-normal response for higher stimulus intensities. To quantify this parameter, the pre- and post-experimental input–output curves were compared.

The main problem was the shortening of the post-experimental input–output curve due to the upward shift in threshold while the maximum audiometer output remained the same. The compromise chosen was to cut the upper part of the pre-experimental input–output curve, in order to reduce it to the length of the post-experimental one. Disregarding the shift in threshold the post-experimental curve was superimposed on the pre-experimental one and the distance on the dB scale common to both curves was divided into three equal parts; the slopes of each third of the two curves were then compared. The $\log_{10}$ of the area enclosed between the AP function and the dB axis was calculated and compared for the corresponding thirds of the two curves. Significant differences between the areas were observed, the post-infusion area being bigger (1st third, $t = -1.78$; 2nd third, $t = -1.84$; 3rd third, $t = -2.27$; $P < 0.05$).

Scala media pO_2 *measurements*

Continuous pO_2 measurements were made during the whole experiment and recorded graphically. The stabilized pO_2 reading, obtained after the electrode had penetrated the scala media and before the blood infusion was started, was taken as the normal reference level and considered to be 100% oxygenation. Reduction from this level was calculated as percentage of decrease from normal.

The mean level of pO_2 in mmHg before infusion was 34.55 (range 27–42). A rapid decrease in pO_2 which followed the switching off of the respirator for a few

TABLE II

DISTRIBUTION OF ANIMALS ACCORDING TO THE PERCENTAGE OF DECREASE IN COCHLEAR pO_2 CAUSED BY INFUSION OF NORMOVISCOUS OR HYPERVISCOUS BLOOD

Reduction in pO_2 (%)	No. of animals	
	Normal-viscosity blood	Hyperviscous blood
0– 9	10	—
10–19	4	—
20–29	1	3
30–39	2	2
40–49	3	5
50–59	—	3
60–69	—	3
70–79	—	2
80–89	—	2

seconds, and a return to the reference level after the air had been turned on for some time after a short overshoot, indicated that the preparation was good and that the blood infusion could be started.

Infusing blood with normal hematocrit and viscosity but pO_2 of 30 mmHg caused slight but variable reductions in the scala media oxygen pressure, as can be seen in Table II. The average reduction for the whole group was 15.27% with a standard deviation of 17.89. The average measured level was 29.23 mmHg.

Measurements of the pO_2 in the scala media were made after hyperviscous blood was infused, which followed the removal of an amount of blood equal to that to be infused from the right cannula. This was done only if the reference pO_2 level obtained before the first infusion of blood was reached again.

Infusion of the cochlea with hyperviscous blood with 30 mmHg pO_2 caused a decrease in the oxygen level in the scala media in all the animals. The average pO_2 decrease for the whole group of 20 animals was 53.35% with a standard deviation of 18.74, and the mean pO_2 level measured was 16.12 mmHg.

Statistical analysis of the results using the Wilcoxon test for two dependent groups demonstrated a significant difference between the cochlear pO_2 resulting from infusion with normal-viscosity blood with 30 mmHg pO_2, and that induced by the infusion of hyperviscous blood with the same level of oxygenation; the reduction induced by the hyperviscous blood was significantly greater ($t = 6$; $P < 0.001$).

Discussion

Hearing loss due to cochlear hypoxia caused by impairment in blood flow occurs frequently. It is generally accepted that in most cases of sudden deafness the etiological factor is interference with the cochlear blood supply. It has been estimated that 40000 new cases of hearing loss due to impairment in cochlear blood flow are registered every year in the U.S.A. [24]. Other investigators [14,15] have stated that 54% of patients suffering sudden deafness had decreased coagulation times, and that even in cases in which the etiology of sudden deafness was proven to be viral, the mechanism involved was probably intravascular thrombosis due to hypercoagulation.

Presbyacusis, or 'old age deafness', is a very slow, progressive deterioration of hearing. In a certain percentage of the population, however, it can start early in life, or its benign course may change drastically when a concomitant impairment in cochlear blood flow occurs. A malignant evolution of hearing loss in presbyacusis [21] has been associated with thickening of the hyaline portion of the walls of the spiral vessel and of the stria vascularis in the lower half of the basal turn of the cochlea. Fisch et al. [9] also reported finding an association between impairment of cochlear arterial blood flow and sudden deafness.

Hearing loss due to occlusion of cochlear blood vessels is not always permanent if the critical decrease in cochlear blood perfusion is temporary. For example, reversible bilateral sensorineural hearing loss was reported in a young patient with sickle-cell anemia [28]. Hearing impairment of short duration could be related to a

temporary obstruction of cochlear vessels by red cells sludging during the severe crisis period. A partial hearing loss [25,29] was reported to have occurred in a patient with macroglobulinemia; this patient recovered hearing acuity with improvement in the hyperviscosity syndrome. Aggregate formation and dissolution is a normal process [22] but exaggerated frequency or magnitude of red cell aggregation is a pathological condition which affects blood viscosity.

In the experiments described in this paper, the cochlear blood supply in guinea pigs was impaired by perfusing the ear with hyperviscous blood. The validity of the methods used to impair blood supply was based on the propensity of blood to flow in a laminar fashion [17]. Due to the stream-lined flow pattern, the blood supplied by the two vertebral arteries does not mix within the common trunk of the basilar artery. The slowdown in the flow of blood through the cochlear vessel caused by the high viscosity of the blood induced hypoxia in the guinea pig cochleas because the oxygen content of the blood previously had been reduced to a 'pre-critical level'.

At this level of oxygenation, the normoviscous blood caused a mild reduction in the scala media pO_2 of 15.2% for the whole group of 20 animals. However, the hyperviscous blood at the same level of oxygenation reduced the pO_2 in the scala media to 53.3%. These findings explain the differences in click-evoked AP measured in cochleas perfused with normoviscous and those perfused with hyperviscous blood. When blood with normal viscosity and pO_2 of 30 mmHg was infused, no changes in AP were observed, but infusion of high-viscosity blood with the same level of oxygenation affected the AP response to sound in 17 of the 30 animals.

One can speculate that normally the cochlea can afford a 15% decrease in the pO_2 level before any alteration is seen in the AP function, but with 53% reduction in pO_2 half of our animals showed impaired AP. The above findings indicate that there is more than enough oxygen in the cochlear blood supply to deal with normal conditions of blood oxygenation; in fact, cochlear blood is hyperoxygenated in order to avoid impairment in function during occasional interruptions in pulmonary ventilation.

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