Red Venous Blood: Occurrence and Significance in Ischemic and Nonischemic Cerebral Cortex*

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The occurrence of bright-red blood (rather than blue or bluish-red blood) in surface veins of the cerebral cortex of man and animals is a striking phenomenon, although it may be overlooked by an unsuspecting or inattentive observer. Red venous blood (RVB) has been seen flowing from normal or abnormal cerebral tissue in a number of situations. Abnormal vessels that pass arterial blood directly into venous channels, such as the shunts that occur in arteriovenous malformations and tumors, frequently are associated with bright-red venous blood.\(^8\) RVB has been seen during and after seizures, whether spontaneous or induced by electrical stimulation\(^9\) or chemical stimulation.\(^10\) When cerebral ischemia is relieved, as after the release of a temporary clamp from a cerebral artery in animal studies or during surgery for aneurysms in humans, generalized or focal RVB may develop\(^16\) (Feindel, W., unpublished observations; Sundt, T. M., Jr., unpublished observations). Generalized reddening of cerebral venous blood may occur after the restoration of flow of adequately oxygenated blood following cardiac arrest or after clamping the great vessels or the trachea.\(^11\)

RVB has been noted in human cerebral cortex in veins draining cystic or scarred areas,\(^2,11\) presumably related to earlier cerebral infarction. In addition, RVB has been seen in animals in regions of brain made ischemic by occlusion of a middle cerebral artery.\(^19\) Systemic hypoglycemia, produced by injecting insulin, may cause RVB to develop in ischemic cortex of animals.\(^10\) Because of the implication that venous oxygen saturation is greater than usual, the occurrence of bright-red blood in veins draining ischemic tissue is surprising. In this paper, data about red cerebral venous blood will be presented, and theories about the development of RVB in ischemic cerebral tissue will be reviewed.

Methods

Data from studies of 128 cats and 38 squirrel monkeys have been analyzed. Fifty-four cats were anesthetized with halothane; pentobarbital was used in the other 112 animals. The right middle cerebral artery (MCA) of each animal was exposed by the extradural approach\(^4\) and occluded with a clamp or clip. The surface of the cerebral cortex was exposed bilaterally by craniectomy, and protected with a thin covering of plastic (Saran). The superficial cortical microvasculature was observed through an operative microscope and photographed.\(^19\)

In the 54 cats anesthetized with halothane, regional cortical blood flow (CBF) was measured by digital analysis of the appearance and disappearance at the cortex of the radioactivity of krypton-85 injected in the brachiocephalic artery.\(^17\) Mean systemic arterial blood pressure (MABP) was monitored in each animal with a strain gauge or manometer attached to a catheter placed in the femoral artery. Spontaneous fluctuations of MABP occurred in many animals; additionally, in 24 cats with CBF measurements, MABP was changed by the intravenous injection of phenylephrine (Neo-Synephrine) or sodium nitroprusside.\(^17\) Arterial carbon dioxide tension \((Paco_2)\), arterial oxygen tension \((Pao_2)\), and arterial pH were measured in the 54 cats with CBF measurements. Thirty of these (those that did not have MABP changed) were curarized and ventilated mechanically, and \(Paco_2\) was changed by altering the amount of \(CO_2\) in the inspired air. Hemodilution was studied in 22 squirrel monkeys and seven cats by the intravenous injection of concentrated salt-poor human albumin, low-molecular-weight dextran, 5% dextrose, or physiologic saline solution.\(^15\) Observations and measure-
ments were made from minutes to days after MCA occlusion, and at varying levels of MABP and $\mathrm{PaCO_2}$.

**Results**

*Nons ischemic Cortex.* Nearly anything that was done to the exposed (but otherwise normal) cerebral cortex of the animals could lead to the development of RVB. Removal of the dura after craniectomy in both the cats and the squirrel monkeys was followed by transient reddening of the blood in surface veins approximately three fifths of the time (14 of 23 times in a series of animals in which RVB had been noted as present or absent). After removal of the dura, RVB was generalized, but lasted a few minutes at most.

Undue retraction or pressure on the cerebral cortex, or inadvertent laceration or damage from cautery, could produce RVB that was generalized or focal in the area of damage. Subdural, subarachnoid, or intracerebral hemorrhage, air embolization, and any other similar occurrence often was followed by the development of RVB. None of these invariably produced RVB; whether a given situation would be followed by reddening of venous blood was unpredictable.

Red venous blood did not develop spontaneously in the superficial veins of the nonischemic cerebral cortex of any animal if respiration, blood pressure, and other systemic factors were relatively normal. Likewise, a change of MABP did not produce RVB in any animal. Correspondingly, CBF of nonischemic cortex did not change appreciably with changes of MABP.

When the $\mathrm{PaCO_2}$ was increased, the superficial arterial vessels of the cortex dilated and the CBF increased. In a series of 20 cats, when an increase of $\mathrm{PaCO_2}$ produced a CBF of more than 2.0 ml/gm/min (total of 19 measurements), blood in surface veins invariably was bright red (Fig. 1). When CBF was less than 1.0 ml/gm/min, blood in surface veins invariably was blue (total of 41 CBF measurements). When CBF was between 1.0 and 2.0 ml/gm/min, RVB was uncommon (seen 30 times in a total of 99 measurements). RVB was seen at CBF rates as low as 1.13 ml/gm/min, but not until CBF was more than 1.7 ml/gm/min did the incidence of RVB exceed that of blue venous blood (Fig. 1). When RVB developed in response to an increase of $\mathrm{PaCO_2}$, it was present in all visible cerebral veins (Fig. 2).

**Ischemic Cortex.** After the cerebral cortex of the animals was made ischemic by the occlusion of a middle cerebral artery, RVB could develop within minutes (Fig. 3), or be noted after removal of the dura several days later. RVB that developed spontaneously in an ischemic cortex could be generalized, throughout all visible veins, but more frequently it occurred in only one venous branch or one venous tree. If focal, RVB in one branch of a vein was seen to flow into a larger vein, side by side with blue venous blood from another area of the cortex (Fig. 3). Laminar flow of differently colored blood has also been observed in association with tumors and seizures.

RVB occurring focally in association with ischemia of cortical tissue usually was present in regions where other ischemic changes were developing, or near the periphery of areas of severe ischemia. If RVB was present in areas of cortex that had severe ischemic changes, then it was present also in other surface veins, including veins draining areas of less severe ischemia.

When RVB appeared spontaneously in ischemic cortex, it could be transient, lasting only a few minutes, or could persist to the termination of the experiment as long as 5 hours later. However, once RVB disappeared and blood in the veins reverted to a bluish color, there rarely was a spontaneous recurrence of reddening.

CBF was measured bilaterally 18 times in 10 animals that had RVB develop spontaneously in ischemic cortex. Three of these 18 times RVB was associated with blood flow rates higher than those of the hemisphere opposite the occluded MCA. The other 15 times, however, RVB was present despite CBF rates lower than those of the opposite hemisphere; in two instances RVB was seen when CBF was between 0.20 and 0.30 ml/gm/min.

As with nonischemic cortical tissue, local trauma, surgical damage, or air embolization often was followed by the development of RVB. Similarly, RVB could be produced in ischemic cortex initially, or for a second time in an area in which RVB had been noted previously, by alteration of systemic or local factors. Increasing the MABP produced focal or
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FIG. 1. Occurrence of RVB in nonischemic cortex of 20 cats, related to cerebral blood flow.
CBF was changed by changing $P_{\text{aco}_2}$.

generalized RVB regularly. This was accompanied by an increase of regional CBF to levels above those measured before the blood pressure was increased. An increase of $P_{\text{aco}_2}$ often was associated with the development of RVB in ischemic cortex. When RVB followed an increase of $P_{\text{aco}_2}$, however, regional CBF values could either increase or decrease.

Hemodilution occasionally produced focal or generalized RVB in ischemic cortex. RVB occurring after hemodilution generally was transient, lasting at most an hour or two, but it was accompanied by persistent cerebral edema. In one squirrel monkey, focal RVB developed after papaverine was dropped on the surface of the ischemic hemisphere.

Discussion

The situations in which red venous blood has been observed in nonischemic and in ischemic cerebral tissue are summarized below.

Nonischemic Cortex
1. Increased arterial carbon dioxide tension
2. Relief of anoxia from airway obstruction, cardiac arrest, or obstruction of great vessels
3. Injury to brain or vessels (traumatic, operative, air embolus)
4. Arteriovenous shunts (vascular malformations or tumors)
5. Seizures (spontaneous, or chemically induced, or electrically induced)
6. Relief of ischemia (release of arterial clamp)
7. Scars, cysts

Ischemic Cortex
1. Spontaneous (acute or chronic ischemia)
2. Increased blood pressure
3. Increased arterial carbon dioxide tension
4. Hemodilution (albumin, low-molec-
Fig. 2. Superficial microvasculature of exposed but otherwise normal cerebral cortex of cat. *Upper Left:* 
\( \text{Paco}_2 \) 48 mm Hg; CBF 1.55 ml/gm/min. *Upper Right:* \( \text{Paco}_2 \) 36; CBF 1.05. Note constriction of arterial vessels.  
*Lower Left:* \( \text{Paco}_2 \) 46; CBF 1.46. Arterial vessels have dilated. *Lower Right:* \( \text{Paco}_2 \) 72; CBF 2.48. Note dilatation of arterial vessels, increase in numbers of visible small vessels, and reddening of blood in veins.

Fig. 3. Superficial microvasculature of cerebral cortex of squirrel monkey. *Left:* Before occlusion of middle cerebral artery. *Center:* Four minutes after occlusion. Note dilatation of certain vessels, constriction of others.  
*Right:* Thirty minutes after occlusion. Note reddening of blood in veins, and laminar flow of red and blue blood in larger vein. Note also usual changes of ischemia.
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5. Hypoglycemia
6. Trauma to brain or vessels
7. Local application of vasoactive agents.

Reddening of venous blood implies a higher-than-usual oxygen saturation and, therefore, failure of the tissue drained by the veins containing red blood to utilize all the oxygen made available to it. In the few instances in which blood gases have been measured in RVB, oxygen saturation has been abnormally high. The possibilities for increased oxygen saturation of venous blood include the following: 1) shunting of blood from arterial channels directly to venous channels without passage through capillaries; 2) vasodilatation and increased blood flow, with increased delivery of oxygen in excess of tissue need (hyperemia, reactive hyperemia); 3) damage to the normal aerobic metabolic processes of tissue, so that oxygen is not utilized; 4) blockage of the usual vascular channels, particularly in the capillary net, so that intercapillary distances are increased and diffusion of oxygen is limited to only a part of the tissue; and 5) death of cells and tissue with loss of substance (for example, from injury or anoxia), with maintenance or restoration of the flow of blood through normal channels. Some or all of these mechanisms may be operative in the various situations in which RVB has been observed.

Arteriovenous Shunts. Arteriovenous shunts are not present to any significant degree in normal brain. However, shunting of blood from arterial to venous channels is the mechanism for the occurrence of RVB in association with vascular malformations and neoplasms. The clinical significance of this phenomenon, familiar to neurosurgeons, has been well described. It is unlikely that the “opening up of shunts” is responsible for the development of RVB in normal or ischemic cerebral tissue.

Vasodilatation and Reactive Hyperemia. Local or generalized vasodilatation, with increased blood flow and increased delivery of oxygen to tissue, can be called reactive hyperemia when it occurs in relation to injury, damage or stimulation. The mechanism of reactive hyperemia almost certainly accounts for the occurrence of RVB in normal cerebral cortex after the relief of anoxia or cardiac arrest, after trauma or manipulation of blood vessels, after hemorrhage or air embolization, and after seizures or unusual activity. The specific vascular and neurogenic mechanisms leading to reactive hyperemia in these circumstances are not known, but hypoxia, local accumulation of carbon dioxide and acid metabolites, or direct irritation of blood vessels or their nerves may be responsible.

Reactive hyperemia may account for the development of RVB in ischemic cerebral cortex after local trauma or air embolization. However, another mechanism (such as those discussed later) may be operating to prevent the ischemic tissue from utilizing the additional oxygen made available to it during the state of reactive hyperemia.

 Vasodilatation with increased blood flow (not a form of reactive hyperemia) accounts for the occurrence of RVB in normal cerebral tissue when PaCO₂ is increased. Vasodilatation also may be the mechanism for the development of RVB in ischemic cortex in response to increased PaCO₂ in those cases in which CBF increases. But again, additional mechanisms must be operating when RVB develops in ischemic cortex despite a decrease of CBF.

The failure of RVB to develop in non-ischemic cerebral cortex after an increase of systemic blood pressure probably is a manifestation of autoregulation, indicating a failure of induced hypertension to cause increased blood flow.

Loss of Tissue Substance. Damage to tissue, with loss of the normal number of metabolically active cells but a lesser reduction of vascular channels and blood flow, probably accounts for the occurrence of RVB in association with scars or cystic lesions of the cerebral cortex. With a reduced number of active cells, less oxygen is utilized than usual and some oxygen can be returned to venous channels. In each of the three reported cases of RVB associated with cystic scars (Feindel and Perot's Case 9, Penfield's Cases 20 and 21), the original cause of cortical damage probably was ischemic infarction, but ischemia had cleared by the time RVB was observed.

Red Venous Blood in Ischemic Cerebral Cortex. It is difficult to understand why ischemic tissue does not utilize all the oxygen made available to it, and why veins draining ischemic cerebral cortex at times contain red, oxygenated blood. Of the possible explanations for RVB in ischemic cerebral cortex discussed below none seems entirely satisfactory.
**Vasodilation and “Luxury Perfusion.”** Lassen\(^9\) and Høedt-Rasmussen and associates\(^8\) have proposed that the cortex giving rise to RVB is not actually ischemic, but that focal hyperemia occurs either in the periphery of an ischemic zone or after an improvement of perfusion. They feel that the accumulation of carbon dioxide and other acid metabolites produces vasomotor paralysis, failure of autoregulation, vasodilatation, and increased blood flow: the “luxury-perfusion syndrome.” Corollary evidence supporting this theory is the angiographic demonstration of early filling of veins and “capillary blushing” near cerebral infarcts,\(^2\) phenomena which have now become generally recognized and which may occur in up to 35% of patients studied within a few days of infarction. Additional evidence is obtained from studies of regional cerebral blood flow in humans and animals in which flow rates near ischemic or infarcted tissue occasionally are found to be “supernormal,” that is, above the normal values for that tissue,\(^5\) or above the values obtained from analogous regions of the opposite, nonischemic hemisphere at the same time, as in the studies reported here. Further support for “supernormal” flow as an explanation for RVB in ischemic cortex is obtained from autoradiographic studies\(^4,18\) in which foci of increased blood flow have been found near ischemic areas in autoradiographs of brains of animals injected with \(^14\)C-antipyrine.

Yet, RVB, early venous filling, and blushing are not always associated with supernormal cerebral blood flow. In some human subjects, calculated values for regional blood flow may be higher in areas of blushing and rapid transit of blood than in other areas of the same hemisphere, yet lower than normal.\(^4,8\) Similarly, in our studies, only rarely was RVB from a hemisphere with an occluded MCA associated with blood flow rates higher than those of the opposite, nonischemic hemisphere. It can be argued that the CBF measurements were made from a block of ischemic cortical tissue and that the RVB was coming from nonischemic or less ischemic tissue nearby. However, the techniques used for CBF measurement depend on the clearance of a diffusible radioactive indicator, and thus relatively well-perfused regions of tissue are emphasized in the weighted-average flow values that are obtained. Moreover, in our animal studies, when RVB was generalized, CBF measurements were made directly from the cortex giving rise to RVB.

With more refined methods for the measurement of CBF in humans, and with autoradiographic studies of animals, it may be proved that RVB, early venous filling, and blushing in ischemic brain are always associated with regions of supernormal CBF. If so, the cause of these phenomena will have been reasonably shown to be hyperemia following ischemia or near ischemic or infarcted tissue.\(^8,9\) But “luxury perfusion” may be only relative; that is, blood flow in regions with RVB may be increased only in comparison to the rest of the brain, but less than normal. If supernormal flow is not present, then other mechanisms must be considered to explain why ischemic tissue does not use all the oxygen supplied to it.

**Decreased Oxygen Extraction by Damaged Tissue.** If the normal aerobic metabolic activities of cells are damaged by ischemia, with or without death of the cells, brain tissue will not be able to utilize the oxygen provided to it, and oxygen will remain in the blood, causing RVB. RVB occurring during hypoglycemia probably is produced in this way.\(^10\) If metabolic paralysis, or death of cells, were the cause of RVB in ischemic cortex, however, then RVB should be seen in veins draining the center as well as the periphery of ischemic zones. Likewise, damage to metabolic processes cannot explain early venous filling and blushing demonstrated by angiography in patients with cerebral infarcts. Another possibility, that ischemia changes capillary permeability, producing an interference with the diffusion of oxygen into tissue, seems unlikely.

**Shunting of Blood from Arterial to Venous Channels.** The rapid passage of blood from arterial to venous channels would explain RVB seen in ischemic cerebral cortex. However, arteriovenous shunts are rare,\(^6\) and it is unlikely that the “opening up of shunts” accounts for RVB in ischemic cortex.\(^19\) It is also unlikely that ischemia causes dilatation of capillaries, to produce a type of functional arteriovenous shunt with supernormal flow.

**Partial Blockage of Vascular Network.** If there is blockage of certain channels of the vascular network (capillaries, arterioles, or venules), for example, from aggregation of formed blood elements (“sludging”) or platelet thrombosis due to ischemia,\(^1,19\) effective intercapillary distances may increase. Cells
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near capillaries or thoroughfare channels that remain open may not be able to utilize all the oxygen carried through the open vessels, and remote cells may be too far away to receive oxygen diffusing relatively slowly. Thus, blood flowing through these channels that remain open will still contain abundant oxygen at the venous side of the vascular network, causing RVB. If blood flow through open channels is near normal or greater than normal for those vessels, early venous filling and blushing could be seen in contrast studies. Moreover, even if flow through open channels were greater than normal, flow through the region of tissue would be less than normal, as has been found in our studies of animals. Thus, partial blockage of the vascular network explains all the known facts about RVB in ischemic cerebral cortex.

The finding that RVB can be made to develop in ischemic cerebral cortex by hemo-
dilution or by increasing the mean systemic arterial blood pressure or PaCO₂ can be accounted for either by the theory of focal hyperemia, luxury perfusion, and supernormal regional flow or by assuming partial blockage of vascular channels. All the experimental situations that produce RVB in ischemic cortex of animals can cause increased perfusion, and can increase flow through open channels or can open previously blocked channels. Even when regional blood flow of ischemic cortex decreases with an increase of PaCO₂ (the "intracerebral steal"), as found occasionally in our studies of animals, the appearance of RVB can be explained by increased flow through the periphery of the ischemic zone or through fewer open channels.

Many factors may be operating to cause RVB, early venous filling, and blushing near or in ischemic or infarcted cerebral tissue. The facts can best be explained, however, by focal reactive hyperemia ("luxury perfusion" of Lassen) or partial blockage of the vascular network from "sludging" of blood.

Summary

Red venous blood (RVB) with increased oxygen saturation can be seen in veins draining cerebral tissue in many situations. Increased arterial carbon dioxide tension, relief of anoxia, local trauma, arteriovenous shunts, neoplasms, seizures, cystic scars, and acute and chronic ischemia all can be associated with RVB. Early filling of veins and "capillary blushing," demonstrated with contrast material, also can be associated with cerebral ischemia. The best explanation for RVB in ischemic cerebral cortex is focal hyperemia ("luxury perfusion" of Lassen), or partial blockage of the vascular network from aggregation of formed elements of blood ("sludging"), with flow preserved through fewer channels.

References

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