Erythropoietin as a Volume-Regulating Hormone: An Integrated View

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The intravascular volume consists of 40% to 45% red cells. Their production is controlled predominantly by erythropoietin (EPO), a hormone that is secreted particularly when tissue hypoxia is present. Because of this high percentage of the total intravascular volume the question comes to mind that, in addition to hypoxia, can volume-regulation mechanisms, known to be responsible for the maintenance of plasma volume, modulate EPO secretion when the total vascular volume changes? Indeed, there is evidence that in situations in which the intravascular volume or specifically the intrathoracic volume is altered, EPO secretion is affected. EPO secretion increases when the intrathoracic volume decreases 24 hours after water immersion or after endurance exercise when a negative water balance prevails. A head-down tilt on the other side induces central engorgement leading to a decrease of EPO concentrations. Under these experimental conditions no hypoxia was seen, supporting the idea that a volume stimulus outgoing from intrathoracic parts of the circulation modulated EPO secretion. Further observations from the clinical side are needed to support these ideas and the consequences need to be implemented into clinical practice.
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The antidiuretic hormone (ADH), the hormones of the renin-angiotensin system, and the hormones of the natriuretic peptide family (ANPs) usually are regarded as volume-regulating hormones. These hormones control the salt and water handling of the kidney and thereby the filling volume of the cardiovascular system. At the same time they act on the vascular smooth muscle cells, modulating the size of the vascular bed. As outlined by Gauer and Henry,[1-3] the final goal of volume regulation is not the homeostatic control of the blood volume but the continuous adaptation of the plasma volume (PV) to the ever-changing size of the heart and vascular bed. The regulation of red cell mass (RCM) must be included in these volume regulatory mechanisms because RCM comprises about 40% to 45% of the intravascular volume and therefore should not be ignored in this respect. The

question now is how erythropoietin (EPO) can be included in the feedback loops that were constructed in the past to control blood volume.[3]

EPO as a Volume-Regulating Hormone

We attempt to integrate the EPO secretion mechanisms into the concept of blood-volume regulation by regarding EPO as a volume-regulating hormone (eg, similar to ADH). This means that EPO-secreting mechanisms also should be subject to the needs of the cardiovascular system in addition to the 3 well-known elements of the EPO feedback loop: bone marrow, oxygen sensors, and the kidney endocrine function.[4]

Nowadays it currently is well accepted that as the first line of defense against hypoxia, besides the increase of red cells caused by the secretion of EPO, vasodilation, and angiogenesis, the stimulation of respiration and anaerobic metabolism must be taken into account.[4-6] In the case of vasodilation and angiogenesis, a link between hypoxia defense mechanisms and the cardiovascular system is established that now brings
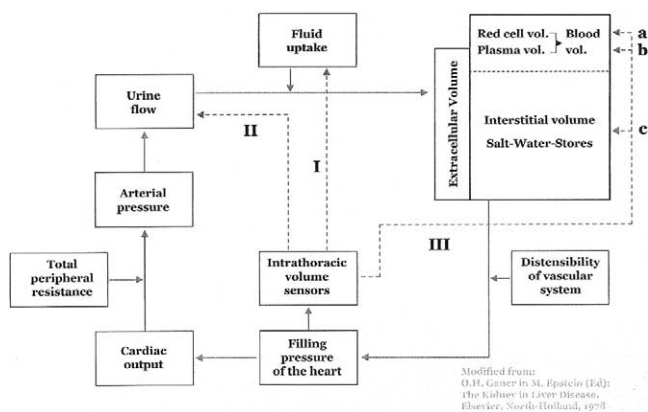
Figure 1 Pathways of volume control according to Gauer and Henry[2] and Gauer[3] as modified from Gauer.[25]

EPO-secreting mechanisms close to the volume-control mechanisms. Angiogenesis and vasodilation affect the absolute size of the vascular bed and also the blood volume and its distribution along the body axis when these mechanisms take place in the peripheral muscles.

The increase of RCM will increase the total circulating blood volume, while at the same time a reduction of the PV occurs. On the other hand the PV does not necessarily have to be reduced when RCM is increased provided that the vascular capacity increases because of angiogenesis and vasodilation. The latter two mechanisms, which are dependent on the induction of inducible nitric oxide synthase and the production of vascular endothelial growth factor,[4] would keep the filling pressure of the system within tolerable limits despite an increased intravascular volume. This points to the fact that indeed EPO regulation should be seen in close conjunction with regulatory mechanisms, as proposed by Gauer and Henry[1] in 1963.

In the concept of Gauer and Henry,[2] the central venous pressure is the parameter by which the filling state of the cardiovascular system can be estimated. In this context the central venous pressure should be seen as a static parameter depending simply on volume (cm³). At the same time, this parameter determines cardiac output via venous return (cm³/min) and, to a limited extend, also the urine output.[2,7]

Pathways for Blood-Volume Control

The basic concept of the feedback loop, as seen in Figure 1, was introduced by Guyton and Coleman[8] and centered around the filling pressure of the heart as the starting point. From here one has to follow the solid lines that lead toward the left to the cardiac output and via the arterial blood pressure to urine flow. The size of the extracellular space would be controlled mainly by a mechanical feedback system.

The routes I, II, and III were introduced by Gauer and Henry[2,3] and later were extended by Gunga and Kirsch.[18] These pathways are activated by subtle changes of the cardiac filling pressure that induce corrections in PV by hormonal

shortcuts in which the autonomic nervous system is involved. The mechanics of the cardiovascular system as part of short-term and long-term adaptations are circumvented. These pathways are activated by volume receptors located in the walls of the atria and the intrathoracic vessels. Within these pathways the earlier-mentioned hormones (ADH, the renin-angiotensin-aldosterone system, and ANPs) play an important role. On one hand these hormones control the salt and water output of the kidneys and on the other hand they act on the vascular smooth muscle cells modulating the size of the vascular bed, keeping the filling pressure of the circulation on a level that allows a proper function of the cardiovascular system. In other words, besides the filling volume of the cardiovascular system, the distensibility of the vessel walls is responsible for the level of the central venous pressure. On the right side of Figure 1, this parameter is included in the basic feedback loop.

Pathway III is subdivided into 3 components: (1) represents the RCM, which by its size is affected by the filling stage of the central parts of the circulation. This is discussed later in more detail. (2) The second component is the well-known branch that controls the salt- and water-excretion mechanisms (called the *Gauer-Henry* reflex). (3) The third component comprises mechanisms that affect the size of the interstitial volume. This mechanism controls the distribution of fluids between the intravascular and interstitial space. In this connection the vasorelaxant effects of the natriuretic peptide family need to be mentioned, which induce a volume shift from the intravascular into the interstitial space and vice versa.[9]

It also must be mentioned here that it is not only the absolute size of blood volume but also the volume distribution between the intrathoracic and extrathoracic parts of the circulation that can have great effects on these volume-regulating mechanisms. In fact, most of the pathways shown in Figure 1, pathway III were studied when volume shifts (ie, by orthostasis) were induced and maintained for longer times. Water immersion or head-down tilt were experimental models used more often for these purposes.[10,11]

Under these experimental conditions, changes of the hormonal secretion patterns of the volume-regulation hormones are described in detail, in addition to the many adaptive mechanisms of the heart and peripheral vessels.[13]

The ADH and aldosterone secretion were reduced when an engorgement of the intrathoracic vessels and heart chambers were induced by immersion or head-down tilt.[10,12] Kamiya et al[14,15] found the sympathoadrenal response to be attenuated during immersion and head-down tilt.[13] The engorgement of the central circulation means that blood volume is available in abundance and needs to be excreted by the kidneys or redistributed into extrathoracic parts of the circulation.[16]

The question now is whether EPO secretion also is affected by those maneuvers, which can be performed at sea level so that hypoxia cannot be responsible for changes in EPO concentrations.

Indeed, Gunga et al[17] showed that head-down bed rest conditions, which maintained central engorgement, led to a

significant decrease of EPO concentrations in human beings. When the patients were allowed to get up at the end of the study, EPO levels significantly increased.[17,18] In all likelihood this was caused by the decreased intrathoracic filling volume because it is known that total blood volume is reduced and blood pooling in the lower limbs is enhanced after such a bed rest period. Both mechanisms should lead to a reduced cardiac filling volume with a reduced central venous pressure. Similar results were obtained by Ehmke et al[19] in dogs. The stimulation of EPO secretion was most effective when experimental procedures were combined with decreased central venous pressures.

In the same direction speak observations made after a marathon race. Three hours after the race EPO values were found to be increased, and EPO values were increased even more after 32 hours. It is known that under these conditions, especially days after the race, hypoxic stimuli cannot be responsible for these findings. In all likelihood, a decreased central venous pressure explains these findings because fluid loss caused by the race was not yet restored completely. Central venous pressure monitors the filling state of the intravascular space and activates all mechanisms restoring the fluid content of the intravascular space. EPO seems to be one of the possibilities for such a long-term adaptation.[17,18]

Similarly, increased EPO levels 24 hours after water immersion must be interpreted in the same way. After immersion, patients are volume depleted because of the high urine output during the immersion periods. This volume depletions lasts for more than 24 hours combined with low central venous pressures.[10]

All experimental models leading to long-lasting increased EPO values have in common a decreased central venous pressure. Hypoxic stimuli can be excluded because all experiments were performed at sea level. This definitely supports the hypothesis that EPO secretion can be modulated by mechanisms known to control fluid balance.

Because the hormones mentioned so far have clear-cut effects on vascular smooth muscle cells either increasing (ANPs) or decreasing the vascular capacitance (ADH and angiotensin), the question remains as to which effect EPO has in this respect. From clinical observations it is known that in some patients under EPO treatment hypertension might develop. A direct effect of EPO on smooth muscle cells was excluded by the authors.[20-23] It seems to be clear now that with EPO administration hypoxic vasodilation disappears. With the absence of hypoxic vasodilation, together with increasing hematocrit levels, increased blood pressure can be explained. A direct effect of EPO on the vascular smooth muscle cells can be shown only with extremely high EPO doses.[21] In this respect EPO apparently cannot be compared with other volume-regulating hormones.

Still another indirect effect of EPO on blood pressure should be mentioned. When the intravascular volume is increased the central venous pressure can be increased. This was seen in trained athletes.[24] This could induce, via pathway IIIc in Figure 1, a relaxation of vascular smooth

muscle cells shifting volume into the interstitial space and pooling blood in extrathoracic parts of the circulation. In this way, EPO might affect volume distribution within the body, acting indirectly as a volume-regulating hormone. However, at the moment this is a matter of speculation and needs to be proven experimentally.

These effects should come into play when the volume shifts between the intrathoracic and extrathoracic parts of the circulation take place and are maintained for a longer period of time. In our opinion, there are good reasons to regard EPO as a volume-regulating hormone.

References

1. Gauer OH, Henry JP: Circulatory basis of fluid volume control. Physiol Rev 43:423-481, 1963
2. Gauer OH, Henry JP: Neurohormonal control of plasma volume. Int Rev Physiol 9:145-190, 1976
3. Gauer OH: Role of Cardiac Mechanoreceptors in the Control of Plasma Volume. "Osmotic and Volume Regulation." Munksgaard, Alfred Benzon Symposium XI, 1978, pp 229-247
4. Lappin TRJ: Classification and consequences of anemia, in Jelkmann W (ed): Erythropoietin: Molecular Biology and Clinical Use. Johnson City, TN, E.P. Graham Publishing Co., 2003
5. Hochachka PW, Gunga H-C, Kirsch K: Our ancestral physiological phenotype: An adaptation for hypoxia tolerance and for endurance performance? Proc Natl Acad Sci U S A 95:1915-1920, 1998
6. Jelkmann W (ed): Erythropoietin: Molecular Biology and Clinical Use. Johnson City, TN, E.P. Graham Publishing Co., 2003
7. Guyton AC, Jones CE, Coleman TG: Circulatory Physiology: Cardiac Output and its Regulation. Philadelphia, W.B. Saunders, 1973
8. Guyton AC, Coleman TG: Longterm regulation of the circulation: Interrelationships with body fluid volumes, in Reeve EB, Guyton AC (eds): Physical Bases of Circulatory Transport; Regulation and Exchange. Philadelphia, W.B. Saunders, 1967, pp 179-201
9. McDowell G, Shaw C, Buchanan KD, et al: The natriuretic peptide family. Eur J Clin Invest 25:291-298, 1995
10. Epstein M: Renal, endocrine, and hemodynamic effects of water immersion in humans, in Fregly MJ and Blatteis CM (eds): Handbook of Physiology—Environmental Physiology. New York, Oxford University Press, 1996, 845-853
11. Fortney SM, Schneider VS, Greenleaf JE: The Physiology of Bed Rest, Handbook of Physiology-Environmental Physiology. New York, Oxford University Press, 1996, pp 889-939
12. Ameln von H, Laniado M, Röcker L, et al: Effects of dehydration on the vasopressin response to immersion. J Appl Physiol 58:114-120, 1985
13. Iwase S, Mano T, Saito M: Effects of graded head-up tilting on muscle sympathetic activities in man. Physiologist 30:S62-S63, 1987
14. Kamiya A, Iwase S, Kitazawa H, et al: Baroreflex control of muscle sympathetic nerve activity after 120 days of 6° head-down bed rest. Am J Physiol 278:R445-R452, 2000
15. Kamiya A, Iwase S, Sugiyama Y, et al: Vasomotor sympathetic nerve activity in men during bed rest and on orthostasis after bed rest. Aviat Space Environ Med 71:142-149, 2000
16. Mano T, Iwase S, Saito M, et al: Somatosensory-vestibular-sympathetic interactions in man under weightlessness simulated by head-out water immersion, in Hwang JC, Daunton NG, Wilson VJ (eds): Basic and Applied Aspects of Vestibular Function. Hong Kong, Hong Kong University Press, 1988
17. Gunga HC, Kirsch K, Baartz F, et al: Erythropoietin under real and simulated microgravity conditions in humans. J Appl Physiol 81:761-773, 1996
18. Gunga HC, Kirsch KA, Roecker L, et al: Erythropoietin regulation in humans during exercise and in extreme environments, in Jelkmann W (ed): Erythropoietin: Molecular Biology and Clinical Use. Johnson City, TN, E.P. Graham Publishing Co., 2003

19. Ehmke H, Just A, Eckardt K-U, et al: Modulation of erythropoietin formation by changes in blood volume in conscious dogs. J Physiol 488:181-191, 1995

20. Eckardt K-U: Cardiovascular consequences of renal anaemia and erythropoietin therapy. Nephrol Dial Transplant 14:1317-1323, 1999

21. Heidenreich S, Rahn KH, Zideck W: Erythropoietin induces contraction of isolated renal small resistance vessels. Nephrol Dial Transplant 5:739-740, 1990

22. Mann JFE: Hypertension and cardiovascular effects—long term safety and potential long-term benefits of r-HuEPO. Nephrol Dial Transplant 10:80-84, 1995

23. Raine AEG, Roger SD: Effects of erythropoietin on blood pressure. Am J Kidney Dis 18:76-83, 1991

24. Convertino VA, Mack GW, Nadel ER: Elevated central venous pressure: A consequence of exercise training-induced hypervolemia? Am J Physiol 260:R273-R277, 1991

25. Gauer O: in Epstein M (ed): The Kidney in Liver Disease. North Holland, Elsevier, 1978