Arterial Chemoreceptor Reflex and Hypertension

Andrzej Trzebski

In this issue, Fletcher et al. report that repetitive brief hypoxia applied during a 7-hour period per day for up to 35 days causes diurnal elevation of blood pressure in rats. This significant finding examines the mechanism of chronic, reversible arterial hypertension correlated with sleep apnea syndrome.\textsuperscript{2-4} The hemodynamic pattern of obstructive sleep apnea (OSA) (blood pressure rise at the nadir of arterial blood oxygen saturation $[\text{SaO}_2]$ and bradycardia or bradyarrhythmias with secondary ventricular tachyarrhythmias\textsuperscript{5,6}) mimics those of the circulatory chemoreceptor reflex response in the absence of breathing and lung inflation.\textsuperscript{7}

To interpret diurnal elevation of blood pressure after periods of brief hypoxic episodes, recent progress in the elucidation of functional characteristics of arterial chemoreceptors should be considered. In contrast to rapidly adapting baroreceptors, chemoreceptors proved to be facilitated by prolonged hypoxic stimulation.\textsuperscript{8,9} Consequently, resetting of the arterial chemoreceptor reflex is opposite to that of the baroreceptor reflex. In this regard it is surprising that arterial chemoreceptors were long considered irrelevant to hypertension, quite opposite to baroreceptors, which have been and still are a classic field of study in hypertension research. A contribution of the arterial chemoreceptor reflex to mechanisms of primary hypertension was recognized late.\textsuperscript{10-13} Apparently, the reason for the low level of interest was a common observation that in healthy normoxic subjects, chemoreceptor reflex drive seemed not to influence resting blood pressure and sympathetic activity, unlike ventilation, which is significantly dependent on peripheral chemoreceptor drive. More recently, however, it has been shown in rats that abrupt hyperoxic inactivation of arterial chemoreceptors induced a transient fall of arterial blood pressure\textsuperscript{14} and of some sympathetic activity.\textsuperscript{15} Sympathoexcitatory chemoreceptor reflex drive may be of significance in aged rats,\textsuperscript{16} possibly contributing to an increase in sympathetic activity with aging.\textsuperscript{17}

Carotid bodies are significantly enlarged in human hypertensive subjects\textsuperscript{18-21} and in spontaneously hypertensive rats (SHR),\textsuperscript{22} mainly in primary but not in renal hypertension.\textsuperscript{22} Also the level of norepinephrine and dopamine, modulatory factors in chemotransduction mechanism, is higher in carotid bodies of SHR\textsuperscript{23} and of Lyon hypertensive rats\textsuperscript{24} as compared with matched normotensive strains. Although the relation of morphological alterations within the carotid bodies to blood pressure level is still debated and strain-related dependence seems more important,\textsuperscript{22} one fact should not be overlooked. The only other condition in which adaptive increase in size and growth of carotid bodies has been demonstrated is chronic hypoxemia,\textsuperscript{21,25} with prolonged excitation of arterial chemoreceptors.

A possible role of arterial chemoreceptors in functional mechanisms of primary hypertension has been inferred in several ways. The following changes have been observed in SHR: increased sensitivity to hypoxia of carotid body afferent activity\textsuperscript{26} and hyperventilation\textsuperscript{27} dependent on peripheral chemoreceptors augmented resting drive.\textsuperscript{28} These findings correspond to results obtained in humans: increased ventilatory and pressor responsiveness to isocapnic hypoxia in young subjects with mild hypertension,\textsuperscript{13} augmented resting ventilatory drive dependent on peripheral chemoreceptors in hypertensive subjects\textsuperscript{29} and in normotensive subjects with a family history of hypertension,\textsuperscript{30} and potentiation of excitatory sympathetic nerve responses to hypoxia in borderline hypertensive subjects.\textsuperscript{31} In young humans with early mild hypertension, chemoreceptor reflex drive contributes slightly to elevated resting blood pressure as an abrupt hyperoxic deactivation of chemoreceptors produces a brief, transient fall of blood pressure and total peripheral resistance,\textsuperscript{29,30} preceding pressor response due to peripheral hyperoxic vasoconstriction.\textsuperscript{32} In contrast, in renal hypertension in rabbits similar alterations in carotid body chemoreceptor reflex function were not observed.\textsuperscript{33}

One can hypothesize that long-term, repetitive episodic hypoxia during OSA resets chemoreceptor reflex drive to a higher level and initiates hypertension. Consistent with this view is a recent finding that hypertensive OSA patients demonstrate an augmented ventilatory response to brief hyperoxic inactivation of arterial chemoreceptors (the decrease in ventilation) as compared with OSA subjects without accompanying hypertension.\textsuperscript{34}

On the other hand, an augmented chemoreceptor reflex drive in hypertension may facilitate instability in breathing,\textsuperscript{35} which promotes sleep apnea.\textsuperscript{36} Thus, a kind of vicious cycle between sleep apnea syndrome and primary hypertension may develop.\textsuperscript{37}

Recently, hypoxemia has been challenged as attributable to postapneic hypertension\textsuperscript{38} since prior supplementation of oxygen and attenuation of hypoxemia during OSA to a mean of 90% $\text{SaO}_2$ did not prevent apneic rise in blood pressure. Mild hypoxia (80% $\text{SaO}_2$) applied during non—rapid eye movement (NREM) sleep without apnea did not elevate blood pressure.\textsuperscript{39}
However, both arguments overlook strong enhancement of hypoxic chemoreceptor stimulations in OSA by accompanying hypercapnia. Both chemical stimuli act according to a multiplicative and not additive function.\(^{39-41}\) The contribution of hypoxemia alone, calculated by regression analysis of blood pressure to \(Sao_2\), indicated that about 30% of OSA-induced blood pressure elevation was dependent on hypoxemia.\(^{6}\) Whatever the quantitative contribution of hypoxemia alone and in combination with hypercapnia, the main functional meaning of chemoreceptor reflex in OSA remains as the arousal response that terminates both sleep and apnea.\(^{42-43}\) Chemoreceptor-induced arousal and resumption of breathing initiate secondary changes like tachycardia, increases in venous return, and intrathoracic mechanical factors, which combine to affect the blood pressure rise during and immediately after apnea.\(^{38}\)

The time has long passed since the chemoreceptor reflex was regarded as a bulbar neuronal circuitry controlling solely respiratory and cardiovascular effectors.\(^ {44}\) Chemoreceptor stimulation releases catecholamines from adrenal medulla in rats; this is the only mechanism by which hypoxia activates adrenomedullary gland.\(^ {45}\) Arousal was observed as early as 1955\(^ {46-47}\) and, like "defense response,"\(^ {48}\) is an important pattern of suprabulbar organization of the chemoreceptor reflex.\(^ {44}\)

Figure 1 shows a block diagram of some other factors related to chemoreceptor stimulation considered within the complex mechanisms of hypertension. Attention should be given to a new proposed mechanism: increased tissue oxygen supply due to chemoreceptor-dependent hyperventilation.\(^ {49}\)

Tissue hyperoxia is a local vasoconstrictor factor\(^ {50}\) responsible for an increase in total peripheral resistance and blood pressure both in humans and experimental animals (for example, see References 29, 30, and 32). Some findings support the hypothesis for a role of oxygen supply in hypertension.

Average tissue oxygen tension in resting spinotrapezious muscle does not differ between normotensive Wistar-Kyoto (WKY) rats and \(SHR,^{31}\) yet the vasoconstrictor response of arterioles to oxygen is significantly enhanced in SHR.\(^ {52-53}\) Much wider distribution of oxygen tension in hypertensive compared with normotensive rats suggests a temporary and a permanent microvascular rarefaction.\(^ {51}\) Rarefaction, especially in lower body musculature and in the intestinal wall, has been frequently reported in SHR.\(^ {54-56}\) Vascular rarefaction was found also in humans with established hypertension.\(^ {57-58}\)

A question arises concerning why rarefaction of the vascular musculature does not induce tissue hypoxia despite normal organ blood flows in hypertension. One of the possibilities is an increase in blood oxygen-carrying capacity. Indeed, polycythemia-augmented blood cell volume and hematocrit were reported in SHR\(^ {59}\) and in human essential hypertensive patients.\(^ {60}\) Association of polycythemia with hypertension was observed as early as 1905\(^ {61-62}\) and influenced Volhard and Fahr\(^ {63}\) in their first distinction of essential ("red") and renal ("pale") hypertension. Coincidence between high hematocrit and hemoglobin content and various kinds of hypertension has been frequently reported since.\(^ {64}\)

The view that augmented blood viscosity in polycythemia accounts for elevated blood pressure\(^ {65}\) has been
recently challenged. Polycythemia induced by erythropoietin therapy is associated with hypertension, not attributable to augmented blood viscosity.66 In this regard a most significant finding appears to be the prevention and retardation of hypertension in anemic sideropenic SHR kept for 14 weeks on a low-iron diet from 3 weeks after birth (prehypertensive stage). This remarkable antihypertensive effect of sideropenic anemia is not entirely reversible after return to normal diet. In contrast, in normotensive rats no hypotensive influence of low-iron diet occurs, and the drop in hemoglobin content and hematocrit is less significant than in SHR.67 Oxygen delivery in hypertension is potentiated by facilitated oxygen dissociation since the content of 2–3 diphosphoglycerate in erythrocytes, both in SHR and young human hypertensive subjects, is augmented.49

It has been suggested that rarefaction of microvasculature in hypertension is in part attributable to excessive oxygen supply.12,45,67 Tissue oxygen tension appears as a variable controlled by short-term functional autoregulation and long-term structural remodeling of microvasculature in hypertension. Accelerated onset of hypertension in SHR exposed to systemic hypoxia is consistent with this concept.58

The functional role of microcirculation has been assessed by approximate calculation of the contribution of the microvasculature to total peripheral resistance elevation in hypertension: it gives a significant figure up to 20% compared with about 40–60% overall increase in total peripheral resistance in SHR.69 Control of precapillary resistance is shifted from the larger to smaller vessels, and in sustained hypertension the contribution of microvessels to total peripheral resistance is augmented.49

As an important modulator of intrinsic smooth muscle activity and angiogenesis,52,53,70 tissue oxygen at the level of the microcirculation potentiates a functional and structural autoregulation according to the classic concept of Folkow.71

Adaptive oxygen-dependent response in microvasculature explains the long-debated controversy72 in interpretation of the antihypertensive influence of chronic hypoxia in SHR and among people who live at high altitudes73,74 despite excessive peripheral chemoreceptor stimulation. Microvasculature adaptation to low oxygen supply by proliferation of microvessels59 is opposite to rarefaction in hypertension. Microvascular adaptation in chronic hypoxia dominates and prevents hypertension-dependent rarefaction.75 A similar mechanism of structural adaptation of microvasculature to excessive, chronic oxygen demand in skeletal muscle has to be considered as a factor attributable to the antihypertensive effect of long-term physical exercise.77

Some other mechanisms have been proposed as protective in chronic hypoxia: suppression of salt appetite in SHR exposed to chronic hypoxia78 and a humoral natriuretic effect of prolonged chemoreceptor stimulation.72 The last mechanism may limit its antihypertensive effect due to hemococoncentration and increase in oxygen-carrying capacity of blood (Figure 1). Recently some doubts have been raised as to hypoxia-induced natriuresis in rats. Acute hypoxia produced an antinatriuretic and antidiuretic effect that was not abolished by bilateral denervation of kidneys.79

Hypertension related to sleep apnea syndrome made clear that interaction between the circulatory and respiratory systems deserves attention in considering mechanisms of hypertension.

Guyton's concept of circulation80 is based on the priority to maintain an optimal blood flow balance with volume control and variable blood pressure. Increase in total peripheral resistance represents a negative feedback to protect against tissue overflow. In line with this concept, volume sensors of the body play a decisive role in homeostatic mechanism. We postulate that a parallel priority is to maintain an optimal tissue oxygen tension. Microvascular adaptation in hypertension can be regarded as a negative feedback preventing excess tissue oxygen. For this homeostatic mechanism, oxygen sensors of the body are necessary. Arterial chemoreceptors are oxygen sensors unique in the sense of initiating integrated respiratory and autonomic nervous system circulatory adjustments to subserve this priority. Such an integrative approach to hypertension is still at the beginning stage. Isolated results have not been noted by documented functional links, and many relations remain hypothetical. Yet, this new avenue may provide useful information on the mechanisms of hypertension.

References

74. Hultgren HN: Reduction of systemic arterial blood pressure at high altitudes. Adv Cardiol 1970;5:49–53

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A Trzebski

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