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REVIEW ARTICLE

Heart-Lung Acting Together

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Introduction

Most frequently medical education treats the pulmonary system and the cardiovascular system separately. And this is, indeed, quite understandable because each system's pathologies and their treatments differ in so many ways. However, from another perspective, the physiologist's, both systems are the evolutionary product for capturing oxygen from the external environment and delivering it to the mitochondria in the body's cells for the generation of the energy needed for life's operations. Bound together for maintaining life, the cardiopulmonary system is in fact two sub-systems composed of two pumps (diaphragm and heart) and two sets of collapsible tubes (airways and vasculature).

Systems Interacting

Interestingly, each subsystem mechanically influences the other. For example, increasing blood pressure, acting via the high pressure arterial baroreceptors, acts to brake the neural output from the sympathetic nervous system (SNS). Heart beat will decrease. But so also will respiration. Brunner and her colleagues [1] found in anesthetized dogs that raising pressure in the carotid sinus from 100 mmHg (where the respiratory frequency was 9.1 min^{-1} and minute ventilation was 4390 mL min^{-1}) to 200 mmHg, respiratory frequency fell to 4.8 min^{-1} and minute ventilation to 3180 mL min^{-1} Contrariwise, in the hemorrhagic state pressure on the baroreceptors has been reduced, and thus neural input from the baroreceptors to the nucleus of the solitary tract (NTS) and then on to the nuclei of the SNS is reduced, removing the "brake" on the SNS. Cardiac frequency and contractility will increase. So also does respiration. The same study [1] showed that when the pressure in the carotid sinus dropped to 50 mmHg, respiratory frequency increased to 9.7 min^{-1} and minute ventilation increased to 4530 mL min^{-1} [1].

The increase in respiratory action physically generates more negative intrathoracic pressures. This makes for a lowering of the downstream pressure for venous return. Simultaneously the increased SNS output both increases cardiac activity and generates a peripheral vasoconstriction, producing an increase in total peripheral resistance. Increased SNS output also decreases capacitance of the venous system. This effect squeezes more blood into the circulation contributing to an increase in venous return, heightened by the lowered downstream venous pressure. The increased cardiac output and peripheral resistance combine to increase perfusion pressures throughout the hemorrhagic victim.

Both systems use the same peripheral neurological receptors: carotid body, carotid sinus, aortic baroreceptors. In human subjects' aortic chemoreceptors are not usually operating. The receptors' pathways to the CNS are via afferent neuron pathways in cranial nerves IX and X to the NTS in the medulla [2,3]. The reflex responses of the heart and vasculature are via the SNS. One must keep in mind that the chemoreceptors and the baroreceptors have exactly the opposite effect on the SNS output. Baroreceptor traffic acts to brake SNS output, whereas chemoreceptor traffic accelerates SNS output. Fibers from the carotid sinus in most species run over and through the carotid bodies to join fibers exiting from the carotid body to form the branch of cranial nerve IX. So, the same nerve is carrying activity to the CNS which is to have the exact opposite effect on SNS output.

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Pulmonary Pathologies

Pathologies in one system can also influence the functioning of the second. For example, obstructive sleep apnea (OSA) occurs with a collapse of the upper airway muscles for various reasons. Obesity is one clear risk factor. During the apneic interludes of OSA, metabolism, of course, continues.

Hence, PaO_2 begins to fall and $PaCO_2$ begins to rise. This combination is a powerful stimulus to the carotid bodies [4-7]. As a consequence, SNS neural output increases. Arterial blood pressure increases. The somnolent subject awakens momentarily to take in a quick breath, and the cardiovascular variables begin to return towards normal. But since episodes of OSA can occur as often as eight to 10 times per hour, blood pressure often does not return to the normal level. Nocturnal hypertension results; and this condition sometimes carries over into daytime hypertension.

In Chronic Obstructive Pulmonary Disease, COPD, the patient is usually hypoxic because of faulty gas exchange. which is due to airways collapse upon expiration and the diminished alveolar surface for gas exchange (emphysema). This leaves some amount of gas trapped in the alveoli. The alveoli do not undergo complete ventilation. The trapped gas mixes with some amount of new air to yield an alveolar PO_2 of significantly less than the normal PAO_2 of 97-99 mmHg. This, of course, lowers arterial values (PaO_2) to the 60-70 mmHg range, a strong stimulus for the carotid bodies. In some animal models [8-10] this stimulus reduces the well-known hypoxic pulmonary vasoconstriction (HPV). HPV puts a load on the right ventricle. And increased right ventricular load can produce fluid accumulation in the lungs, legs, ankles, and can sometimes end in right heart failure. But this sequence is certainly dependent on the severity of the disease and the age of the subject. Some emphysema patients are not only hypoxic but can carry a $PaCO_2$ value of greater than 60 mmHg, respiratory acidosis. However, other adaptive mechanisms in the kidney come into play involving the retention of bicarbonate in the plasma while the H^+ is returned to the filtrate. This keeps pH_a from becoming too acidotic.

Cardiovascular Pathologies

More recent studies of the effects of chronic heart failure (CHF) in animal models have reported a central role of the carotid bodies (CBs) in that condition [11]. The CBs become more sensitized. The mechanism seems to be the systemically reduced blood flow in CHF includes reduced blood flow in the CBs. This reduces shear stress on a mechanical receptor embedded on the luminal surface of the CBs' vascular endothelial cells. The reduction of shear stress thereon reduces the level of Kuppel-Like Factor 2 (KLF2) in the CBs [12]. This reduces the level of eNOS and of NO in the CBs. In animal models NO is well known to reduce the CBs' neural output [13], in part due to NO's ability to reduce the release of two excitatory neurotransmitters, ACh and ATP, from the CBs' glomus cells [14,15]. But in CHF breathing is also changed. The ventilatory response to hypoxia is increased, and a Cheyne-Stokes pattern is also observed during resting ventilation [16]. Denervation of the CBs abolishes these changes [17]. But this is clearly a radical procedure.

Hence, other remedies in animals were tried; for example, a modest exercise program [18]. Exercise increased cardiac output and systemic blood flow, re-establishing sheer stress in the CBs' vasculature. KLF2 levels went back towards normal bringing the levels of NO back towards normal. Likewise, the inclusion of statins [19] in the diet increased the levels of KLF2 and subsequently levels of NO.

Human Clinical Studies

A 56-year-old male, who had presented with acute heart failure (NYHAII) underwent a unilateral removal of the CB [20]. And six months later he showed that his heart rate variability had subsided, his apneas and dyspneas were reduced, and he had an increase in exercise capacity. In a second study six men suffering from CHF were measured before and one month subsequent to bilateral CB removal (CBR) [21]. After CBR the ventilatory response to hypoxia was reduced by 91%; systolic blood pressure slope, by 71%; diastolic blood pressure slope, by 59%. Heart rate showed no change.

Further, longevity among CHF patients showed that those with heightened CB sensitivity had only a 41% 3-year survival rate whereas those CHF patients without the heightened CB sensitivity had a 3-year survival rate of 76% [22].

CHF subjects have the added challenge to their status in the form of particulate matter (PM) air pollution. CHF patients exposed to elevated ambient PM levels are estimated to be at a 4-fold higher risk of heart trouble compared with healthy subjects [23]. CB involvement is clear because of their increased sensitivity generating increased output from the sympathetic nervous system (SNS). A recent study in a murine model explored the mechanisms of whereby PM pollution put the CHF population at even greater risk. The CB tissues of the CHF mice showed PM-mediated marked inflammatory, oxidant stress, and ion channel gene dysregulation. Pro-inflammatory molecules are well known to increase Ca^{2+} flux in the glomus cells of CBs sensitizing their response to hypoxia. These authors concluded that it was likely that the autonomic alterations in the CHF mice are influenced by PM-mediated up-regulation of Na^+ channels, the Na^+ -Ca^{2+} exchanger, and down-regulation of K^+ channels in CB tissues.

Key Cardiopulmonary Receptor and Anesthetics

From the above it is clear that the CBs play a critical role in controlling the two subsystems. A frequent condition in which their role must be appreciated is in

surgery where a general anesthetic is used frequently in conjunction with a muscle relaxant. This combination can sometimes render a patient emerging from surgery hypoxic and hypoventilating. In general, most anesthetics blunt the neural output from the CBs in response to hypoxia. For example, in some animal studies vecuronium seemed to block CB neural output by blocking nicotinic ACh receptors on the glomus cells of the CB and on the afferent neuron abutting the glomus cell. In the case of the glomus cell vecuronium could have blocked the entrance of calcium needed for the release of ACh and ATP, two of the excitatory neurotransmitters in these cells. In the case of the afferent neuron vecuronium could have blocked the nicotinic ACh receptors [24].

Halothane also depresses CB neural output by enhancing TASK-like K^+ channels in the rat glomus cell. This shut down of channel is thought to be critical for the initiating of the depolarization of the glomus cell [25]. Studies in other species report the same effect of halothane on CB neural output [26]. And as we have seen, reducing CB neural output reduces input to and output from the sympathetic nervous system. Heart, vasculature, lung are clearly yoked to each other mechanically and neurophysiologically.

Clearly, a proper understanding of the appropriate pharmacology to be used in the treatment of heart and lung disease requires a separate presentation of each system. But seeing their interaction would surely result in a deeper appreciation of the complex unity of the cardiopulmonary system's role in organismal survival.

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