Paradoxical Bradycardia during Exercise and Hypoxic Exposure*

The Possible Direct Effect of Hypoxia on Sinoatrial Node Activity in Humans

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We describe a patient with pulmonary emphysema who developed paradoxical cardiodeceleration not only during incremental exercise associated with hypoxemia but also during progressive hypoxic challenge. Since coronary angiogram revealed no abnormality, this unique phenomenon seemed to be due to the direct effect of hypoxia on the sinus node activity.

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The natural response of the sinus node to progressive hypoxia or to incremental exercise is a gradual increase in the heart rate. Even in those with sinus chronotropic dysfunction, the heart rate usually increases, although the maximal sinus rate attained is less than the normal subject. A recent report documented a case with paradoxical sinus slowing during exercise due to coronary perfusion insufficiency. We herein present a patient with chronic obstructive pulmonary disease (COPD) who developed similar cardiodeceleration despite a normal coronary angiographic study, not only during incremental exercise associated with hypoxemia but also during progressive hypoxic challenge. This case may contribute to a better understanding of the direct effect of hypoxia on the sinus node function in humans.

CASE REPORT

A 60-year-old man was admitted to the hospital for evaluation of increasing dyspnea on exertion. Physical examination of the cardiovascular system revealed no remarkable findings. He was not cyanotic but had moderately clubbed fingers. The breath sounds were diffusely weakened. The ECG at rest was normal. The chest roentgenogram displayed hyperinflation and diffusely attenuated vascular markings. Resting arterial blood gas analysis while breathing room air resulted in a pH of 7.40, PaCO₂ of 41 mm Hg, and PaO₂ of 58 mm Hg. A pulmonary function test demonstrated combined severe obstructive and mild restrictive impairments in ventilation: VC, 2.64 L (74 percent of predicted); FEV₁/FVC, 46

![Graph](image-url)
percent, with increased TLC (6.91 L, 119 percent) and decreased Deo (4.3 ml/min/mm Hg, 25 percent). He was diagnosed as having pulmonary emphysema. A cardiac catheterization study revealed the resting hemodynamics to be heart rate of 81 beats/min with regular rhythm, systemic blood pressure of 117/73 mm Hg, pulmonar capillary wedge pressure of 6 mm Hg, mean pulmonary arterial pressure of 20 mm Hg, cardiac index or 3.7 L/min/m², and pulmonary vascular resistance index of 472 dyne•sec•cm⁻².

An exercise test using a bicycle ergometer was performed. The protocol consisted of a stepwise increment of workloads by 12.5 W every 3 min. The expiratory gas was analyzed to calculate minute ventilation every 15 s and SaO₂ was monitored by a finger-tip oximeter. The first test was performed while breathing room air (Fig 1). Resting minute ventilation was 6.4 L/min and then increased progressively up to 28.7 L/min. The heart rate was 77 beats/min initially and increased gradually up to 90 beats/min at 4 min. Thereafter, when SaO₂ decreased below 90 percent, the heart rate suddenly decelerated and finally dropped to 50 beats/min at 6 min (his maximal tolerance). Blood pressure increased from 117/73 to 189/118 mm Hg. Even during this deceleration period, ECG recordings showed normal sinus rhythm without AV conduction block or any obvious ischemic findings in any leads. He reported severe dyspnea but no chest compression feelings. At the end, serum epinephrine and norepinephrine increased from 124 to 380 pg/mL and from 439 to 1,170 pg/mL, respectively. The same exercise was then performed while inhaling 100 percent O₂ (Fig 2). A nearly normal sinus response was restored and his heart rate reached a maximum of 106 beats/min at 8 min. However, a slight deceleration was again observed at the end, although SaO₂ was maintained above 96 percent throughout the test.

On another day, hypercapnic and hypoxic ventilatory response tests were performed to evaluate the chemoreceptor function. During hypercapnic ventilatory response (HVR), PaCO₂ was gradually raised over 6 min until 60 mm Hg, while PaO₂ was maintained over 150 mm Hg. For hypoxic ventilatory response (HVR), SaO₂ was gradually lowered over 5 min down to about 90 percent, while PaCO₂ was maintained at the resting value. The HVR value was 0.88 L/min/mm Hg and HVR was 0.24 L/min/percent, both of which appeared within normal limits. On HCVR,

![Figure 2](image2.png)

Figure 2. Exercise test while inhaling 100 percent O₂. A nearly normal heart rate response was restored. However, a slight deceleration was still observed at the end. For abbreviations, see Figure 1.

![Figure 3](image3.png)

Figure 3. Isocapnic progressive hypoxic test. Note a sudden heart rate deceleration near the end of the test, while ventilation increased steadily throughout the challenge. PrTPO₂ = end-tidal PO₂; PrTPO₄ = end-tidal Pco₂; V_e = minute ventilation; Ti = inspiratory time; Te = expiratory time; HR = heart rate.

The heart rate consistently increased from 52 to 67 beats/min. On HVR, it initially increased from 74 to 87 beats/min, but then suddenly decelerated as SaO₂ fell below 85 percent, and finally dropped to 50 beats/min when SaO₂ was 80 percent (Fig 3). ECG at that time showed neither AV block nor obvious ischemic findings in any leads.

A coronary angiographic study revealed no significant organic stenosis in the right and left coronary artery. The sinoatrial (SA) node branch was intact. Respiratory heart rate fluctuations were fairly good. Carotid sinus massage and an Aschner maneuver lowered the heart rate from 66 to 54 beats/min and from 68 to 52 beats/min, respectively. Intravenous administration of 0.5 mg of atropine increased his heart rate from 70 to 103 beats/min. The ambulatory ECG, monitored for 24 h, showed that the minimal heart rate was 63 beats/min. There were 512 supraventricular ectopics per day, but no ventricular ectopics or ST level changes at all. Electrophysiologic study of the SA node was not performed.

**DISCUSSION**

This patient developed cardiodeceleration only when he was exposed to O₂ desaturation. Although the same phenomenon was observed during exercise, a nearly normal sinus response was restored if the test was performed while inhaling 100 percent O₂. Therefore, the most likely mechanism to explain this unique phenomenon is a direct or indirect effect of hypoxemia. Not only a variety of neural reflexes mediated through various receptors in the cardiovascular or respiratory systems, but also the electrophysiologic activity of the SA node itself could be affected by hypoxia.

An impairment of the blood supply to the SA node may explain the sinus slowing by a direct effect of ischemia. It
may involve an indirect effect of ischemia evoked by the Bezold-Jarisch reflex. In the present case, however, the paradoxical bradycardia is hard to explain only by impairment of coronary perfusion, since an angiographic study revealed normal blood supplies to all branches and no ischemic ECG changes were observed, not only during hypoxic challenge but also during exercise. Therefore, this patient was different from the case documented in the recent report. The pattern of his heart rate changes during incremental exercise or progressive hypoxia was an initial increase and then a sudden deceleration at a point when SaO₂ fell below 85 percent or 90 percent. While inhaling 100 percent O₂, the same phenomenon was still observed to some extent, despite sufficient systemic oxygenation. Thus, a regional tissue hypoxia around the SA node, which is disproportionately severe compared with systemic hypoxemia, is most likely to be responsible for the paradoxical bradycardia in this case. It may reflect the direct inhibitory action of hypoxia on cardiac pacemaker activity that has been shown experimentally in other species or indirect effect of hypoxia mediated through such mechanisms as local production of adenosine.

Exercise-induced coronary spasms in the absence of fixed organic stenosis may be involved, although this alone cannot entirely explain the observed phenomenon, since it was also evidenced during hypoxic challenge without exercise.

In general, the SA node activity is continuously modulated by afferent inputs from various peripheral receptors. The indirect effect of hypoxia on the SA node function is mediated through interactions of several opposing influences. In humans, the stimulation of carotid bodies usually causes cardiac slowing, which effect is modulated by adverse cardioacceleration mediated through pulmonary stretch receptor (PSR) stimulated by hyperventilation. During hypoxic exposure, the heart rate usually accelerates if ventilation is allowed to increase, since PSR activation overrides the direct effect of carotid bodies. Aortic chemoreceptors probably contribute to cardioacceleration during hypoxic exposure, although they may play a minor role in humans.

The carotid body function of the present case must be intact, since he showed a good ventilatory response during hypoxic challenge. Thus, decreased efficacy of the PSR-mediated reflex due to emphysema, decreased activities of the aortic bodies due to chronic hypoxemia, and hyperreactivity of the carotid bodies specific to the heart rate response may also have been involved in the cause of the bradycardia. A marked increase in arterial blood pressure as a consequence of hypoxemia and severe dyspnea may contribute to an additional slowing through arterial baroreceptor stimulation. However, the observed response seems difficult to explain only by these neural mechanisms. First, at least in the initial course of both exercise and HVR tests, there was a gradual cardioacceleration; second, vagal cardiac reflexes reflected in respiratory sinus rate fluctuation or the sinus response to atropine infusion were fairly good; and third, the heart rate steadily increased in parallel with ventilation during the hypercapnic challenge.

Regardless of the mechanisms involved, the paradoxical cardiodeceleration in response to hypoxia must be clinically quite disadvantageous, particularly when subjects are exposed to severe O₂ desaturation. In those patients with COPD, it is serious and potentially lethal, since their O₂ transport is impaired to various degrees due to decreased O₂ uptake in the lung. Therefore, this unique phenomenon should be kept in mind when one sees patients such as those with COPD who are potentially exposed to acute hypoxemia due to an exacerbation of the underlying disease.

REFERENCES


Malignant Lymphoma in a Patient with Relapsing Bronchiolitis Obliterans Organizing Pneumonia*

Santiago Romero, M.D.; Concepcion Martin, M.D.; Bartomeu Massuti, M.D.; Ignacio Aranda, M.D.; and Luis Hernandez, M.D.

A case of relapsing bronchiolitis obliterans organizing pneumonia complicated by malignant lymphoma (four years after the diagnosis) is reported in a 58-year-old woman. To our knowledge, such an association has not been described previously in detail in the literature.


**BOOP = bronchiolitis obliterans organizing pneumonia; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; EBV = Epstein-Barr virus; HTLV = human T-cell lymphotropic virus; NHL = non-Hodgkin's lymphoma; TBB = transbronchial biopsy**

Bronchiolitis obliterans organizing pneumonia (BOOP) is a clinicopathologic entity in which intraluminal fibrosis of distal airspaces is the major pathologic feature. The etiology is often unknown. As in other cryptogenic disorders, multiple associated conditions have been mentioned. Although coexistent lymphoma has been reported, we were unable to find a previous complete description of this association. The patient whose case is reported herein suffered from both conditions over a six-year period.

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