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Review Article

Respiratory Alkalosis as a Therapeutic Target in Cardiac Rehabilitation for Dysautonomia: Mechanisms and Applications

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Abstract

Infective endocarditis (IE) is the infection of inner endothelial layer of the heart including the heart valves and it may present as rapidly progressive or manifest itself as subacute or chronic disease. The epidemiology of infective endocarditis has been changed over the past few decades and the incidence of IE in children in United States and Canada is 1 in 1,250 pediatric hospital admissions in the early 1980s. Atleast 70% of infective endocarditis in children occurs with congenital heart disease whereas rheumatic heart disease in southern states of India and the degenerative mitral valve disease (myxomatous, mitral valve prolapse) in the western countries are the most underlying predisposing conditions to infective endocarditis in adolescents. The characteristic lesion of infective endocarditis is 'vegetation' and a'large' vegetation > 10 mm in size has been reported with an incidence 15.9-62.5% of patients. The significance of vegetation size has been a subject of discussion for many years to predict the embolic episodes. Background of this case study illustrated the varying size and shape of giant vegetation attached to the anterior leaflet of mitral valve in an underlying rheumatic mitral valvulitis and its consequence of valve damage such as chordal rupture, flail leaflet and mitral regurgitation with a description of anatomic features and echocardiographic manifestations in a 10-year-old female child.

Keywords: rheumatic mitral valvulitis; infective endocarditis; giant vegetation; flail leaflet; mitral regurgitation; ping-pong mitral stenosis

1.Introduction

Dysautonomia encompasses a spectrum of disorders characterized by dysfunction in autonomic control, involving the sympathetic, parasympathetic, and enteric nervous systems. Clinical manifestations vary depending on the etiology, the affected neurotransmitter, and the anatomical region involved.

Among the most common subtypes are postural orthostatic tachycardia syndrome (POTS) and vasovagal syncope. Both present with symptoms such as orthostatic hypotension, reflex bradycardia or tachycardia, exercise intolerance, and recurrent syncope episodes [1].

Cardiac rehabilitation has demonstrated benefits in autonomic regulation, and in this context, the modulation of blood pH through respiratory alkalosis could represent an innovative strategy [2,3].

Pathophysiology of Respiratory Alkalosis and Its Relationship with Dysautonomia Respiratory alkalosis is an acid-base disorder characterized by a decrease in the partial pressure of carbon dioxide in arterial blood, resulting in an increase in blood pH above 7.45. This alteration occurs due to an increase in alveolar ventilation, leading to excessive elimination of CO_2 [4,5]. Respiratory alkalosis can cause cerebral vasoconstriction, changes in neuromuscular excitability, and alterations in hemoglobin's affinity for oxygen, thereby influencing tissue oxygenation. Its presence is associated with hyperventilation states under various physiological conditions such as physical activity and exercise at different intensities, and pathological conditions including anxiety, hypoxia, liver failure, and early sepsis [6,7].

Respiratory alkalosis, occurring due to hyperventilation, induces effects on the central nervous system, including changes in neuronal excitability and

modulation of sympathetic tone [7]. In patients with dysautonomia, hyperventilation induced through guided breathing exercises may enhance baroreceptor sensitivity, reduce sympathetic activity, and improve cerebral perfusion, thereby decreasing syncope episodes and improving orthostatic tolerance [6,8].

Daily physical activity and exercise, depending on intensity, have distinct effects on ventilation and pH regulation in patients with dysautonomia [9]. In healthy individuals, increased ventilation during exercise maintains acid-base balance through compensatory mechanisms, but in people with dysautonomia, the ventilatory response may be disproportionate, promoting respiratory alkalosis and exacerbating daily-life symptoms [10,11].

Mild/Moderate/Intense Exercise

During mild-intensity exercise, ventilation tends to increase proportionally to metabolism without significantly reducing $PaCO_2$. However, in patients with dysautonomia, an inefficient ventilatory response with disproportionate hyperventilation is common, which may induce mild respiratory alkalosis even with minimal exertion. This phenomenon may explain the disproportionate fatigue and sensation of dyspnea experienced even during routine activities such as walking or standing for extended periods [11,12].

In moderate-intensity exercise, the increase in alveolar ventilation is greater and may lead to a more marked decrease in $PaCO_2$ in patients with dysautonomia. Due to autonomic hyperreactivity, these individuals may hyperventilate excessively, causing respiratory alkalosis that leads to symptoms such as dizziness, amaurosis, and paresthesias.

Additionally, cerebral vasoconstriction induced by alkalosis can reduce cerebral blood flow, contributing to orthostatic intolerance and predisposition to syncope in these patients [10–12].

In vigorous-intensity exercise, the increase in CO_2 production at the muscular level usually counteracts respiratory alkalosis in healthy individuals, as the ventilatory threshold induces hyperventilation more aligned with metabolic demand. However, in patients with dysautonomia, ventilatory regulation may be erratic, with episodes of inappropriate hyperventilation followed by prolonged periods of hypocapnia. This may not only precipitate exercise intolerance and dyspnea but also worsen day-to-day autonomic instability, promoting anxiety states, reflex tachycardia, and postural intolerance [13].

In daily life, the persistence of respiratory alkalosis induced by episodic hyperventilation in response to minimal efforts may lead to a perception of chronic weakness, impaired regulation of cerebral blood flow, and increased frequency of autonomic symptoms. This phenomenon underscores the need for strategies within cardiac rehabilitation that modulate ventilatory control, promote more efficient breathing, and reduce autonomic hyperactivity in these patients [13,14].

Post-Exercise Ventilatory and Autonomic Response

In patients with dysautonomia, the post-exercise recovery period is a critical phase in which autonomic regulation is challenged, and respiratory alkalosis induced by hyperventilation may play a key role in symptom emergence. During recovery, cardiovascular and ventilatory compensation mechanisms do not follow the same dynamics as in healthy individuals, which may result in symptoms such as dizziness, extreme fatigue, dyspnea, and a sensation of orthostatic instability [15].

After exercise, ventilation should gradually decrease to restore acid-base balance and CO_2 homeostasis. In patients with dysautonomia, however, hyperventilation often persists longer than necessary due to impaired autonomic modulation, prolonging respiratory alkalosis.

Sustained hypocapnia can cause symptoms such as dyspnea, paresthesias, blurred vision, and difficulty concentrating. Furthermore, cerebral vasoconstriction induced by hypocapnia may contribute to post-exercise dizziness and orthostatic intolerance, increasing the risk of syncope or presyncope [15,16].

Exercise induces blood flow redistribution, with an increase in cardiac output and peripheral vasodilation. In healthy individuals, post-exercise recovery involves a gradual decrease in cardiac output and normalization of peripheral vascular resistance to maintain stable blood pressure. In patients with dysautonomia, however, autonomic nervous system dysfunction may result in persistent vasodilation or an inadequate vasoconstrictive response, leading to post-exercise hypotension. This hemodynamic response may be exacerbated by respiratory alkalosis, as hypocapnia further reduces vascular tone and compromises cerebral perfusion [16,17].

Contributing Factors to Hypocapnia

- **Altered baroreflex resetting**: Patients with dysautonomia exhibit deficient baroreflex responses, hindering blood pressure stabilization after exercise and exacerbating orthostatic symptoms.
- **Fluctuations in sympathetic and parasympathetic activity**: The transition from a state of elevated sympathetic activation during exercise to a recovery phase with parasympathetic predominance is irregular in these patients, potentially leading to reflex tachycardia or inappropriate bradycardia.
- **Exacerbated sensitivity to pH and CO_2**: An abnormal ventilatory response to changes in blood pH makes these patients more prone to reactive hyperventilation episodes where sustained hypocapnia diminishes baroreceptor sensitivity, prolonging cardiovagal response and maintaining symptoms longer [17,18].

Foundations of Cardiac Rehabilitation Applied to Dysautonomia

A cardiac rehabilitation program aims to improve patients' quality of life and prognosis. Concurrent training for individuals with dysautonomia is based on combining aerobic and resistance exercise within the same session to enhance autonomic stability, cardiovascular regulation, and functional capacity. In these patients, autonomic nervous system dysfunction results in disproportionate responses to exertion, such as postural tachycardia, orthostatic intolerance, and syncope episodes. Therefore, training planning must incorporate strategies that minimize these adverse effects and support progressive adaptation [16].

Program design begins with a comprehensive evaluation to determine each patient's hemodynamic and ventilatory profile. The cardiopulmonary exercise test is a key tool for identifying exercise tolerance thresholds and detecting abnormal ventilatory patterns through gas exchange curves

(oxygen and carbon dioxide), providing insights into metabolic system behavior. Orthostatic tests, such as tilt-table testing or heart rate variability measurement, are also included to assess sympathetic and parasympathetic tone. Additionally, dysautonomia-specific questionnaires help evaluate quality of life and symptom severity [17].

Aerobic training is implemented with a gradual approach, using low-impact activities such as recumbent cycling, rowing, or treadmill walking with controlled incline. The goal is to improve orthostatic tolerance and optimize cardiovascular efficiency without triggering hyperventilation or postural hypotension. Sessions begin at low intensities, prioritizing diaphragmatic breathing, with careful progression to avoid abrupt blood pressure drops at the end of exertion. Resistance training complements aerobic work by strengthening skeletal muscles, particularly in the lower limbs, thereby improving venous return and stabilizing blood pressure. Exercises focus on multi-joint movements with light resistance and slow, controlled execution, avoiding Valsalva maneuvers that may trigger syncope or dizziness [18,19].

Ventilatory Control

Throughout the program, ventilatory control is essential to prevent exacerbation of respiratory alkalosis. Guided breathing techniques and biofeedback assist in regulating respiratory rate, preventing excessive fluctuations in pCO_2, which reduces the likelihood of symptoms such as dizziness, fatigue, and paresthesias. Post-exercise recovery is managed progressively, with controlled transitions from supine to upright positions and rehydration strategies to stabilize intravascular volume [17].

Medical supervision and continuous monitoring allow for adjustments in training intensity according to each patient's response. With this approach, concurrent training becomes an effective tool to improve functionality, reduce extreme variability in cardiovascular responses, and enable better adaptation to effort in the daily lives of individuals with dysautonomia [16,17].

Mechanisms Involved in the Improvement of Patients with Dysautonomia

The physiological mechanisms involved in ventilation and autonomic regulation that are modified through concurrent training in cardiac rehabilitation for dysautonomia include the optimization of ventilatory control, stabilization of baroreflex response, and modulation of sympathetic-parasympathetic balance. These changes contribute to a reduction in dysfunctional hyperventilation, improved orthostatic tolerance, and greater hemodynamic stability in daily life [11,12].

As previously explained, in patients with dysautonomia, disproportionate hyperventilation leads to respiratory alkalosis and cerebral vasoconstriction, which may cause symptoms such as dizziness, fatigue, and blurred vision. Through controlled breathing techniques and biofeedback, the tendency toward hyperventilation is reduced, promoting a more efficient ventilatory pattern that minimizes fluctuations in the partial pressure of CO_2. This adjustment enhances cerebral oxygenation and reduces the frequency of autonomic crises triggered by hypocapnia [16,17].

Stabilization of the baroreceptor reflex is another key mechanism in symptom improvement. In individuals with dysautonomia, the baroreflex is less effective in regulating blood pressure, contributing to episodes of orthostatic hypotension and reflex tachycardia. Aerobic and strength training facilitate improved baroreflex sensitivity, allowing for a more appropriate response to postural changes and physical exertion. Regular physical activity enhances vascular adaptation to exercise, reducing the amplitude of blood pressure fluctuations and lowering the risk of syncope or presyncope after exertion [16].

Autonomic balance modulation is another relevant effect of training. In dysautonomia, the sympathetic nervous system is often overactive or poorly regulated, contributing to episodes of tachycardia, exercise intolerance, and chronic fatigue. As parasympathetic response strengthens and sympathetic hyperactivity decreases, patients experience a lower predisposition to postural tachycardia, which promotes better quality of life and greater endurance for daily activities [17].

Rehabilitation and Attenuation of Respiratory Alkalosis

Cardiac rehabilitation plays a key role in modulating respiratory alkalosis in patients with dysautonomia by improving ventilatory control, stabilizing autonomic function, and optimizing acid-base regulation. By combining ventilatory control strategies with aerobic and strength training, it helps correct these imbalances and reduce pathological hypocapnia [18].

One of the primary mechanisms involved is the normalization of ventilation through respiratory retraining. In patients with dysautonomia, hyperventilation is often an inappropriate autonomic reflex in response to minimal physical or emotional stress. Through respiratory biofeedback training, respiratory rate control, and supervised diaphragmatic breathing exercises, ventilatory efficiency is improved and excessive CO_2 elimination is avoided. By stabilizing blood pH, episodes of respiratory alkalosis are minimized, reducing the occurrence of symptoms such as dizziness, extreme fatigue, and postural intolerance [8–11].

Aerobic training also plays a crucial role by optimizing chemosensitivity of the respiratory system. Progressive rehabilitation allows for a more physiological adaptation to exertion, reducing the tendency to hyperventilate disproportionately in response to moderate or low workloads. As patients improve their aerobic capacity and ventilatory reflex control, respiratory response variability decreases and CO_2 self-regulation improves, thus reducing symptoms associated with hypocapnia and alkalosis [17].

Another fundamental mechanism is the stabilization of the autonomic nervous system. Cardiac rehabilitation, by improving autonomic regulation through physical exercise, helps reduce sympathetic hyperactivity and strengthens parasympathetic tone, facilitating better ventilatory control, decreasing episodes of reflex hyperventilation, and stabilizing heart rate and blood pressure. This translates to a lower predisposition to respiratory alkalosis induced by minimal stimuli [19].

Finally, improvements in cardiovascular and muscular efficiency also impact ventilatory regulation. A more efficient cardiovascular system, together with strengthened peripheral musculature, enables effective venous return and

better oxygen delivery to tissues without the need for compensatory hyperventilation. In turn, strengthening respiratory muscles enhances ventilatory mechanics, reducing excessive respiratory effort and preventing the activation of inefficient breathing patterns that favor alkalosis [18,19].

Taken together, cardiac rehabilitation corrects abnormal respiratory patterns, optimizes CO_2 self-regulation, and improves autonomic stability, decreasing the frequency and intensity of respiratory alkalosis in patients with dysautonomia. These effects allow patients to experience a lower symptomatic burden in their daily lives and to improve their tolerance to exertion and postural changes.

Assessment of the Response to the Program Using Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is a fundamental tool to evaluate the progression of patients with dysautonomia throughout a cardiac rehabilitation program. By measuring ventilatory, metabolic, and autonomic variables, it is possible to quantify improvements in functional class, reduction of respiratory alkalosis, and tolerance to symptoms during and after exertion [17,18].

Analysis of aerobic capacity is a key point in assessing functional class. An increase in peak oxygen consumption reflects greater efficiency in oxygen transport and utilization, indicating improved exercise tolerance. Similarly, a shift in the anaerobic threshold toward higher exercise intensities suggests that the patient can sustain greater workloads without developing premature fatigue or compensatory hyperventilation. In patients with dysautonomia, the maximum workload achieved during CPET is a sensitive indicator of improvement, as rehabilitation allows for extended time to fatigue and an increase in the number of metabolic equivalents reached without limiting symptoms [19,20].

Ventilatory control is another crucial aspect in evaluating the reduction of respiratory alkalosis. In these patients, disproportionate hyperventilation results in excessive carbon dioxide elimination, leading to hypocapnia and its adverse effects. A decrease in the ventilatory equivalent for carbon dioxide (VE/VCO_2) indicates greater ventilatory efficiency and a lower tendency to hyperventilate in response to exertion. Measurement of end-tidal CO_2 allows monitoring of hypocapnia correction, translating to a reduced predisposition to symptoms such as dizziness, paresthesias, and paradoxical dyspnea. The progressive reduction in the ventilatory equivalent for oxygen suggests that the patient is using their pulmonary capacity more efficiently, reducing respiratory workload and improving exercise tolerance, especially in dysautonomia contexts where hyperventilation is often a major limitation [9,11,20].

Autonomic response and symptom tolerance can also be assessed through CPET. Heart rate recovery after exercise is a marker of autonomic regulation, and its improvement indicates lower sympathetic dominance and more efficient recovery after physical activity. The patient's ability to adequately increase heart rate during exertion is another important parameter, as chronotropic incompetence is a frequent feature in dysautonomia, and its correction through training reflects better cardiovascular regulation. Additionally, recording the perception of dyspnea and fatigue through subjective scales allows identification of improvements in symptom tolerance, which translates to greater functional independence and better quality of life [18,19].

CPET not only provides an objective view of the patient's progression but also enables personalization of rehabilitation and documentation of treatment efficacy. Detailed analysis of aerobic capacity, ventilatory stability, and autonomic regulation allows a clear understanding of how cardiac rehabilitation contributes to symptom reduction in patients with dysautonomia, optimizing their capacity to cope with physical exertion and daily life demands [18,20].

Conclusion: Cardiac Rehabilitation as a Cornerstone in the Management of Dysautonomia

Dysautonomia represents a significant challenge in clinical practice due to patients' inability to efficiently regulate their autonomic response to exertion. Symptoms such as postural tachycardia, orthostatic intolerance, dyspnea, extreme fatigue, and syncopal episodes can severely limit their quality of life, leading to inactivity and progressive deterioration. In this context, cardiac rehabilitation with a concurrent training approach emerges as an effective and safe therapeutic strategy to improve functionality, reduce disproportionate hyperventilation, and stabilize the autonomic response, allowing patients to regain independence and control over their bodies.

The positive impact of cardiac rehabilitation in these patients lies in its ability to optimize ventilatory regulation, improve baroreflex sensitivity, and restore sympathetic-parasympathetic balance. Through specific strategies such as ventilatory control, low-intensity aerobic training, respiratory retraining, and the gradual incorporation of strength exercises, measurable improvements are achieved in exercise tolerance, hemodynamic stability, and reduction of disabling symptoms. Cardiopulmonary exercise testing (CPET) enables objective assessment of each patient's progress, providing physiological parameters that demonstrate the program's effectiveness in terms of oxygen consumption, ventilatory efficiency, and autonomic regulation.

It is time for physicians to recognize cardiac rehabilitation not only as an intervention for coronary diseases but as a comprehensive tool to improve quality of life in patients with dysautonomia. Evidence shows that ignoring autonomic dysfunction and failing to provide appropriate rehabilitation strategies may perpetuate functional disability and medical dependence in these patients. Therefore, referring patients with dysautonomia to specialized cardiac rehabilitation programs is not merely an option but a necessity to transform their prognosis and well-being.

Each patient who enters a rehabilitation program is one step closer to autonomy, functional recovery, and reintegration into a full life. Rehabilitation not only changes numbers and parameters on an exercise test; it changes people's lives. As physicians, our responsibility goes beyond diagnosis and pharmacological prescription—we must provide tools that truly make an impact. Including cardiac rehabilitation in the management of dysautonomia is a decision that marks the difference between limitation and recovery.

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