

Dyspnae after Ten Min Walk in Patients with Preserved Systolic Function

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Abstract:

Background: A widespread, complex complaint that often leads to medical assessment, dyspnea is linked to serious morbidity and unfavorable consequences. A significant percentage of individuals have dyspnea even while their left ventricular ejection fraction is preserved, even though decreased systolic function is a known cause of exertional dyspnea. These individuals' symptoms, which are more indicative of decreased cardiovascular reserve than resting abnormalities, frequently appear following minor physical exercise, like a quick walk. Diastolic dysfunction, modest systolic impairment, chronotropic incompetence, increased pulmonary pressures, and anomalies of the skeletal muscles and peripheral arteries are some of the mechanisms that lead to exertional dyspnea with maintained systolic function. These abnormalities may go undetected by standard resting tests, thus functional evaluation and symptom-based assessment are crucial. It is essential to comprehend the pathogenesis of mild exertion-induced dyspnea in patients with maintained systolic function in order to identify the condition early, develop effective diagnostic techniques, and enhance clinical therapy.

Keywords: Dyspnea; Preserved systolic function; Diastolic dysfunction; Mild exertion; Heart failure with preserved ejection fraction; Exercise intolerance

Introduction:

A wide range of unpleasant breathing-related sensations are referred to as dyspnea, such as chest tightness, a sense of strain or effort, or air hunger, which can be triggered by holding one's breath for an extended period of time (1).

The underlying pathophysiological process can affect the severity and quality of dyspnea, and the patient's social, cultural, and psychological traits can affect how they perceive it. Since acute dyspnea is prevalent in many illnesses, such as infectious, oncologic, and cardiorespiratory conditions, it is one of the primary causes of ED admissions (2).

It is linked to a lengthy hospital stay and a high likelihood of in-hospital mortality, and its severity upon presentation at the emergency department predicts hospital admission. On the basis of scant clinical data, doctors must quickly diagnose patients and determine a course of treatment(3).

Making a differential diagnosis in ED patients with acute dyspnea is a clinical challenge that requires complicated decision-making to reduce hospital mortality and length of stay because prompt and precise therapy can save lives (4).

Pathophysiology:

The basic mechanisms that typically work together to cause dyspnea in patients who visit the emergency department will be the main topic of this talk. Excellent reviews on the pathophysiology of dyspnea are available for a more thorough and organized debate (5).

Hypercapnia/hypoxia

Studies on healthy patients have demonstrated that an increase in arterial pressure of carbon dioxide (PaCO₂) alone can cause dyspnea, despite the initial notion that acute hypercapnia cannot directly cause dyspnea but only causes reflex alterations in respiratory activity (4).

According to earlier research on breath-hold, mild hypoxia marginally increases hypercapnia-induced air hunger, whereas breathing significantly decreases it (1).

abrupt respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), asthma during exacerbations, and abrupt heart failure are among the many conditions that frequently cause an immediate rise in PaCO₂, which may contribute to dyspnea (6).

Acute hypoxia can also cause air hunger, although at least in healthy persons, the drop in arterial pressure of oxygen (PaO₂) needed to produce an unpleasant respiratory sensation is far greater than the 4 mmHg increase in PaCO₂ needed to produce the same effect. Healthy subjects in normocapnic settings only experience air hunger when ventilation is restricted and PaO₂ drops below ~60 mmHg (4).

Mechanical loading

When the elastic or resistive load that the respiratory muscles contract against increases or when the respiratory muscles' capacity to generate pressure is compromised, a perception of greater work of breathing or effort may be elicited. Both respiratory muscle weakness and mechanical disadvantage resulting from a change in the respiratory muscles' operating length, such as in the presence of static or dynamic hyperinflation, can cause a decrease in respiratory muscle performance (7).

Tidal expiratory flow-limitation (EFL), or the incapacity of expiratory flow to increase in response to an increase of driving pressure at isovolume, is a prevalent cause of dynamic hyperinflation in clinical settings (2).

Patients with stable COPD frequently exhibit tidal EFL during resting breathing, and its frequency significantly rises during exacerbations. Dyspnea diminishes when hyperinflation is decreased through medication or physical therapy. In a supine position, tidal EFL is also commonly observed in patients with chronic heart failure (8).

Patients with tidal EFL have more orthopnea, and those with a smaller increase or even a decrease in inspiratory capacity experience a greater increase in dyspnea sensation during the postural change from standing to supine. These findings imply that dynamic hyperinflation is a factor in this perception (9).

Even when standing, tidal EFL may manifest during heart failure decompensation. Acute therapy with diuretics and vasodilators may eliminate tidal EFL and lessen dyspnea in this syndrome (10).

Activation of pulmonary receptors

According to indirect evidence, the development of the dyspnea observed in pathological circumstances marked by pulmonary congestion, the release of local mediators, or parenchymal changes may be related to information transmitted by vagal C and A δ fibers (11).

For example, it has been suggested that alveolitis-induced vagal afferent activity contributes to dyspnea in pulmonary fibrosis. Because it is common in pulmonary thromboembolism (PE), where it can be the only symptom at rest or during exertion, and because it frequently occurs disproportionate to the level of blood gas

alteration, special attention should be given to quick onset dyspnea of unknown etiology. It's interesting to note that the particular feeling of constriction or tightness in the chest that asthmatics frequently experience has been linked to activation of irritant receptors in this condition (12).

Diagnostic evaluation:

Clinical presentation

Since dyspnea is solely self-reported, it should be evaluated independently of other respiratory distress indicators, such as tachypnea or activation of the accessory respiratory muscles, which may also exist without the patient's impression of dyspnea. To improve the diagnosis of the underlying condition, these symptoms should be closely examined in patients who come with dyspnea (2).

The patient's chest wall and abdomen movements should ideally be observed for 60 seconds in order to determine the breathing rate. Healthy adults' resting respiratory rates range from 12 to 22 breaths per minute, with no discernible variation between young and old people. In both respiratory and non-respiratory disorders, these rates rise to varying degrees (13).

When using the quickSOFA score to evaluate a patient in an acute care situation, it is important to consider the wide range of normal respiratory rates. Patients with suspected sepsis are more likely to have poor outcomes if their respiratory rate is more than 22 breaths per minute. Furthermore, the requirement for intubation is independently predicted by a rapid respiratory rate. Acute pulmonary or extrapulmonary restrictive processes, such as pneumothorax, massive pleural effusion, neuromuscular disorders, or discomfort can all be indicated by persistent tachypnea (14).

Since it can be challenging to evaluate rapid shallow breathing in people who breathe on their own, other indicators like "staccato speech" may be useful. Conversely, in cases of decompensated diabetes mellitus, renal failure, or rhabdomyolysis, metabolic acidosis may be the secondary cause of elevated tidal volumes with or without an increased breathing frequency (hyperpnea) (15).

The recession of the tracheal tug and suprasternal fossa suggests increased work of breathing. As pleural pressure swings rise, the suprasternal fossa recedes more, which frequently indicates airway blockage. Examining and feeling the thyroid cartilage will reveal the tracheal tug, which is the result of the trachea moving downward with each inspiratory attempt. It mimics the dragging that the entire mediastinum experiences when the diaphragm contracts forcefully. The Hoover sign, which is an inward shift of the lower rib cage during inspiratory efforts and indicates hyperinflation, may be seen when the intercostal spaces are examined (16).

Additional indicators of increased respiratory effort include nasal flaring, mouth opening, inspiratory laryngeal groans, occipital dorsiflexion (which reflects trapezius contraction during inspiration), and sternomastoid activation during inspiration, which is only present in normal subjects during strong inspiratory efforts (17).

Blood biomarkers:

Various blood biomarkers can provide additional information about the etiology of dyspnea and recommend additional diagnostic testing to help emergency physicians make a differential diagnosis in individuals with the condition (4).

Arterial blood gas analysis

The foundation of clinical care for determining the extent of pulmonary gas exchange abnormalities is the measurement of O₂ and CO₂ tensions and concentrations. A quick diagnostic method for assessing sudden variations in blood pH, PaO₂, and PaCO₂ is arterial blood gas analysis. For patients with acute dyspnea who

arrive at the emergency department, the pH level at presentation is a predictor of both immediate and long-term results. After 12 months, a pH level of 7.39 is linked to a 37% mortality risk in this context (18).

From a diagnostic perspective, patients experiencing acute dyspnea in the emergency department should always have arterial blood gas analysis done, which includes a PaO₂ that provides information on gas exchange. Because arterial and venous pH and HCO₃⁻ readings differ slightly, peripheral venous blood gas sampling may be a good substitute for monitoring purposes under certain circumstances (19).

B-type natriuretic peptide

Together with other clinical and instrumental data, natriuretic peptide (NP) plasma concentrations are advised as the first diagnostic test in acute situations to distinguish between cardiac and pulmonary causes of dyspnea (20).

As lower values rule out acute heart failure, the European Society of Cardiology's guidelines prescribe threshold values of ≥ 100 pg/mL for B-type natriuretic peptide (BNP) and ≥ 300 pg/mL for N-terminal pro B-type natriuretic peptide (NT-proBNP). It should be mentioned, nevertheless, that NPs plasma levels can be impacted by a variety of situations, which lowers the diagnostic precision of these tests. Obesity tends to lower NPs levels, but atrial fibrillation, acute or chronic renal illness, and aging tend to raise them (21).

Troponins and creatine kinase

abrupt coronary syndrome (ACS) should be looked into in all patients who come with abrupt dyspnea, particularly if it is accompanied by chest discomfort. In the diagnosis, risk assessment, and management of these individuals, myocardial biomarkers—ideally high-sensitivity cardiac troponin, or hs-cTn—are a helpful adjunct to clinical evaluation and 12-lead ECG (22).

However, hs-cTn, particularly hs-cTnT, has limited specificity for ACS and can be raised in the presence of sepsis, myocarditis, pericarditis, PE, warfarin usage, and renal failure. It has been demonstrated that different manufacturers perform analytical assays differently, and depending on when symptoms first appear, initial levels of these biomarkers evaluated at ED admission are typically normal. A rise in hs-cTn beyond the 99th percentile of healthy individuals in serial sampling, however, implies myocardial infarction when the clinical presentation suggests myocardial ischemia (23).

Since elevated cardiac troponin levels are associated with increased mortality, measuring them is also crucial for risk stratification in ACS patients (24).

D-dimer:

Following acute thrombus formation, D-dimer, a breakdown product of cross-linked fibrin, rises in plasma due to the simultaneous activation of coagulation and fibrinolysis; however, high D-dimer levels are frequently caused by other common pathological conditions, including infections, inflammation, and cancer (25).

Without additional testing, patients with a negative D-dimer level and a low risk for PE based on a validated grading method (such as the modified Wells criteria) can be excluded from PE. In this sense, the D-dimer cutoff should be modified for age in patients over 50 because the specificity of D-dimer decreases with age. However, a positive result merely means that other diagnostic tests, including CT angiography, which is the primary thoracic imaging test for a definitive diagnosis when PE is suspected, are required (26).

Chest X-ray:

When a patient arrives to the emergency department (ED) with dyspnea, a conventional chest radiograph (CXR) is currently the first routine evaluation done. Despite the possibility of false negative results and the potential for poor agreement between ED doctors and radiologists about CXR interpretation, it is still regarded as the gold standard for diagnosing pneumonia. Because orthostatic standard CXR in two projections can detect even

a small amount of pleural effusion (roughly 50 mL), which is typically only visible at lateral projection in the posterior costophrenic angle, it has long been regarded as the first-line diagnostic tool to be used in the diagnosis and quantification of pneumothorax and pleural effusion (27).

Although interstitial or alveolar edema (such as "Kerley B" lines or peribronchial cuffing), pleural effusion, cardiomegaly, and pulmonary venous congestion all point to a cardiac cause for dyspnea, 20% of patients admitted with heart failure have a non-diagnostic CXR, and other diagnostic methods, like cardiopulmonary ultrasound, can aid in the diagnosis (28).

Ultrasound:

Many declarations and guidelines emphasize on the use of cardiac ultrasonography in the emergency department because of its proven usefulness (29).

Conversely, interest in lung ultrasonography is more recent since, in the past, ultrasonography was not thought to be a suitable technique for imaging the lungs because of the presence of air, which made it difficult to see the pulmonary parenchyma. However, during the past three decades, numerous studies have shown a variety of potentialities of this approach, and many ultrasound findings that were once thought to be artifacts with no clear meaning are now indicators that could aid in the identification of patients who are in critical condition. Since its inception, lung ultrasonography, along with echocardiography, has demonstrated that it is at least as accurate as the standard of care in evaluating a number of illnesses that manifest as acute dyspnea, including heart failure, pneumonia, pleural and pericardial effusion, and pneumothorax. Indeed, lung ultrasonography was able to consistently rule out heart failure as the primary cause of dyspnea in ED patients due to its higher sensitivity for free pleural effusion than CXR and, according to one study, its significant negative predictive value for the condition (30).

Several studies reported that, compared with usual care, cardiopulmonary ultrasound had the advantage of a shorter delay to establish the etiology of acute dyspnea, with an overall high accuracy (> 90%). Last but not least, using chest ultrasonography to triage dyspneic patients outside of hospitals before or during ED transport has improved the appropriateness of interventions and is a promising tool for paramedics, medical technicians, and trained nurses providing pre-hospital diagnosis and care outside of trauma settings (31).

The BLUE-protocol, created by Lichtenstein in 2008, is among the most dependable procedures for the use of lung ultrasonography in the emergency room for the differential diagnosis of acute respiratory failure and, by extension, dyspnea (32).

"Lung sliding" (a twinkle at the pleural line), "A-lines" (repeated horizontal artifacts approximately parallel to the pleural line), and "B-lines" (a distinct comet-tail artifact originating from the pleural line and erasing A-lines) are all evaluated as part of the technique. The mid-subclavicular line, the point immediately crural to the nipple, and the point where the posterior axillary line crosses the horizontal nipple line (PLAPS point–posterolateral alveolar and/or pleural syndrome) were the three points at which lung scans had to be obtained in accordance with the BLUE protocol. In the majority of cases, the protocol's sensitivity and specificity ranged from 90 to 100%, indicating extremely good accuracy in determining the source of respiratory distress (33). Pneumothorax (absence of lung sliding and presence of "lung point," an ultrasound image of the location at which separation by air occurs between parietal and visceral pleura), pleural effusion (presence of liquid between the lung and the parietal pleura), lung consolidation (tissue-like ultrasound appearance of the lung), and interstitial edema (or interstitial syndrome, identified by the presence of vertical artifacts or "B lines") are all ruled out by lung sliding and "A lines." When "lung sliding" and "A lines" are present without deep vein thrombosis, PE is ruled out; however, when the other diagnoses have been ruled out, they may indicate COPD or an exacerbation of asthma as the cause of dyspnea and respiratory failure (34).

However, in recent years, the physical understanding of lung ultrasonography has led to a re-evaluation of patterns like the interstitial syndrome because vertical artifacts, formerly known as "B lines," have different characteristics in various acute and chronic diseases (e.g., lung fibrosis, interstitial edema, interstitial pneumonia, COVID-19 pneumonia, etc.) (30). Figure (1) provides a graphical summary of the primary lung ultrasonography results.

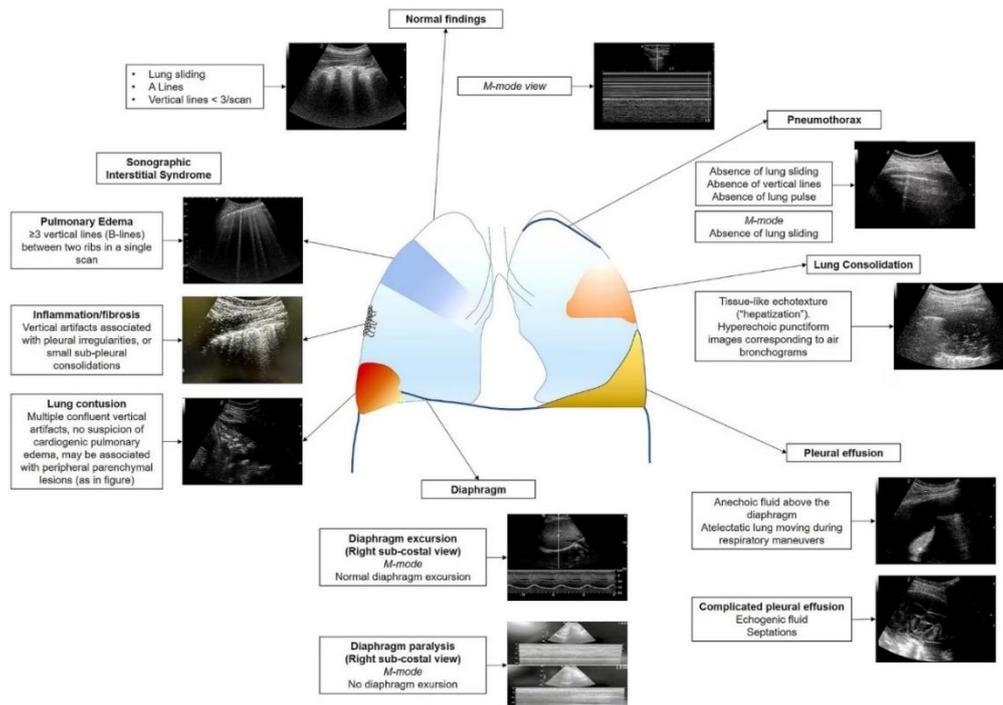


Figure (1): Main normal and pathological findings during lung ultrasound (4).

To improve diagnostic accuracy and reliability, the data from venous ultrasound and echocardiogram (such as left ventricular ejection fraction (LVEF), right ventricular dimensions, and cardiac wall motion anomalies) should be combined with the information from lung ultrasound (35).

Despite the many benefits, the American College of Physicians wisely recommended bedside ultrasound as a potentially useful adjunctive tool for acute dyspnea assessment in emergency departments due to lack of standardization, methodological problems, and the resulting variability among studies in the true positives/true negatives rates of cardiopulmonary ultrasound in the assessment of various conditions (36).

Chest CT

For many pulmonary conditions, such as PE and cancer, chest computer tomography (CT) scanning is the gold standard. Even though there is growing evidence that lung ultrasonography can be helpful, society guidelines currently do not advise using sonography to diagnose pneumonia or pneumothorax; instead, CT and CXR scans are still seen to be more appropriate in these situations (36).

Regarding PE, the CT pulmonary angiography's crucial information is probably the reason for the ultrasound diagnosis's decreased sensitivity when compared to the usual ED evaluation (40% vs. 91%) (37).

A diagram summarizing the diagnostic workup in patients with acute dyspnea is reported in **Figure (2)**.

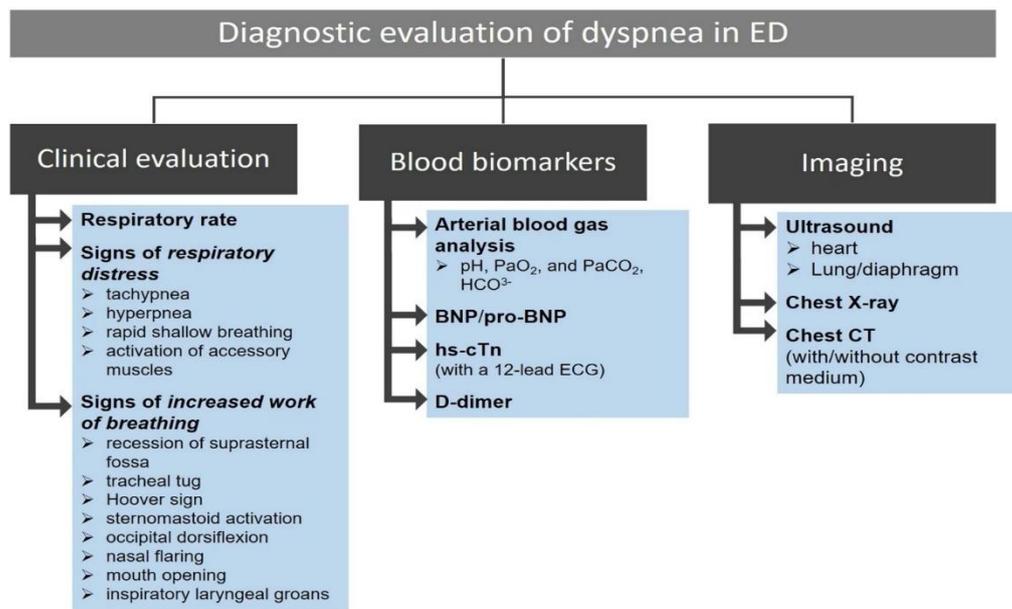


Figure (2): Summary of the diagnostic workup in patients with acute dyspnea presenting at the emergency department. BNP: B type natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; hs-cTn: high sensitivity cardiac troponin; CT: computed tomography; PaO₂: arterial partial pressure of oxygen; PaCO₂: arterial partial pressure of carbon dioxide; HCO₃⁻: bicarbonate (4).

6-Minute Walk Test (6MWT):

A wide range of conditions known as interstitial lung diseases (ILDs) are characterized by lung tissue fibrosis or inflammation. Their most prevalent symptom, exertional dyspnea, is closely associated with a lower quality of life and a lower chance of survival. The six-minute walk test (6MWT), which measures oxygen saturation (SpO₂), dyspnea severity, and six-minute walk distance (6MWD), is frequently used to evaluate functional exercise capacity. Clinical trials commonly employ lower SpO₂ and reduced 6MWD, which are known predictors of death (38).

On the other hand, it is uncertain what exertional dyspnea during the 6MWT means clinically. There is disagreement over how to interpret the Borg 0–10 scale, which is commonly used to quantify dyspnea before and after the test. We performed a systematic review to look at the data and assess the usefulness of exertional dyspnea ratings in this context because of the fundamental role that dyspnea plays in ILD (39).

inadequate proof that increased mortality in ILD is linked to higher post-6MWT Borg scores. There was no trustworthy correlation with oxygen desaturation, and secondary data indicated weak or erratic associations with worse pulmonary function and shorter 6MWD (40).

Previous work has focused more on activity-based scales such as the modified Medical Research Council (mMRC) scale, which predict survival in ILD and COPD, than on direct exertional ratings like the Borg scale. The Borg scale is the most practicable but under-validated alternative because multidimensional tools have been developed but are less useful for everyday use (41).

The self-paced, submaximal character of the 6MWT may be the cause of the erratic correlation between Borg scores and 6MWD. Many patients may not be able to exert themselves to the point where dyspnea inhibits performance, especially those with less severe disease. The comparatively low Borg scores recorded in various studies provide evidence for this (42).

Additionally, there were weak associations found between lung function and Borg ratings. ILD involves several pathways, such as hypoxemia, muscular failure, and cardiovascular reactions, making the relationship

more complex than in airway illnesses, where dyspnea closely correlates with pulmonary function. As a result, rather than overlapping, Borg ratings and pulmonary function probably offer complementing information (43).

Dyspnea After Mild Exertion in Patients with Preserved Systolic Function

Abnormalities in diastolic function are the main cause of exertional dyspnea in patients with maintained systolic function. During activity, the ventricle exhibits either increased passive stiffness, poorer relaxation, or both, which raises the left atrial pressure. At rest, filling pressures might be normal, but even a small amount of effort can reveal the ventricle's incapacity to handle higher preload. This results in a sharp increase in pulmonary venous pressure, which causes congestion and dyspnea (44).

Diastolic Dysfunction

In many individuals with maintained systolic function and exertional dyspnea, poor diastolic filling is the primary problem. The pressure–volume relationship shifts upward during diastole as a result of myocardial stiffness increasing and relaxation being delayed. Although these alterations might not cause obvious symptoms when at rest, left atrial and pulmonary venous pressures rise dramatically due to the increased venous return that comes with even little activity. Shortness of breath and lung congestion are the outcomes (45).

Diastolic dysfunction is caused by a number of cellular and structural processes. Hypertrophy and concentrated remodeling thicken walls and decrease chamber compliance. Myocardial elasticity is further decreased by increased phosphorylation of titin, a crucial cytoskeletal protein, while collagen deposition and extracellular matrix expansion contribute to myocardial stiffness. At greater heart rates, abnormal calcium management makes it harder to relax, especially when demand rises during exercise. Together, these anomalies reduce the ventricle's capacity to support preload without increasing filling pressure (46).

Subtle Systolic Abnormalities

More accurate measurements show systolic reserve deficits even while the ejection fraction is maintained. Early contractile dysfunction is often indicated by diminished longitudinal shortening on strain imaging, particularly in the basal segments. An insufficient increase in stroke volume during effort results from the incapacity to improve systolic performance under stress. When the metabolic needs of activity grow, this slight systolic limitation which is frequently concealed at rest becomes clinically significant (47).

Chronotropic Incompetence

Increased stroke volume and a suitable increase in heart rate are both components of a typical cardiovascular response to exercise. A muted rise in heart rate during exertion is known as chronotropic incompetence, and it is seen in many patients with maintained ejection fraction. This could be a result of intrinsic sinoatrial dysfunction, decreased β -adrenergic sensitivity, or reduced autonomic control. Cardiac output is inadequate when heart rate does not increase sufficiently, especially when stroke volume reserve is already limited. The overall result is exertional dyspnea and early exhaustion during even simple activities like a ten-minute walk. (48).

Pulmonary Vascular and Right Heart Involvement

The pulmonary circulation receives an increase in pulmonary artery pressure retrogradely from elevated left atrial pressure. Increased pulmonary vascular resistance and pulmonary vascular remodeling may exacerbate this over time, resulting in a combination of pre-capillary and post-capillary pulmonary hypertension. Exercise capacity may be further compromised by a subsequent loss in right ventricular function brought on by an increased afterload. Breathlessness is exacerbated and circulatory reserve is limited when the right ventricle, which is especially vulnerable to pressure overload, dilates and has decreased systolic performance (49).

Peripheral and Endothelial Contributions

Patients with maintained systolic function might experience exertional dyspnea, which is not just a heart condition. The involvement of peripheral elements is crucial. Vasodilatory capacity is restricted by endothelial dysfunction, which makes it more difficult for working muscles to adjust blood flow to metabolic demands. Oxygen utilization efficiency is decreased by skeletal muscle alterations such as decreased capillary density, mitochondrial dysfunction, and increased fat infiltration. These anomalies lead to the exaggerated symptoms felt with even mild exertion and lower peak oxygen demand (50).

Clinical Expression During Mild Exertion

Every day, a quick stroll is used to assess cardiovascular reserve. The heart reacts with quick relaxation, improved suction, suitable contractility enhancement, and elevated heart rate in people with normal diastolic and vascular function. Patients with an aberrant reserve but a preserved ejection fraction, on the other hand, show a poor response in a number of domains. Stroke volume plateaus, myocardial stiffness restricts filling, and ventricular relaxation does not quicken. Vascular stiffness and concurrent chronotropic incompetence further reduce the cardiac output response (51).

A sharp and exaggerated increase in left atrial and pulmonary pressure is the result of these anomalies. Patients frequently describe the need to stop or rest after simple activities because they are experiencing dyspnea that is out of proportion to their amount of exertion. When resting measurements seem ordinary, this presentation—which is a characteristic of early HFpEF—provides a crucial diagnostic signal (52).

After light exercise, dyspnea is not only a quality-of-life issue but also a sign of a poor prognosis. It indicates aberrant filling dynamics and shows a compromised circulatory system's capacity to recruit reserve mechanisms. This presentation increases the risk of developing pulmonary hypertension, right ventricular dysfunction, and overt heart failure. Additionally, they are more likely to die, have less functional independence, and be admitted to the hospital (53).

Crucially, objective echocardiographic evidence of severe structural disease frequently appears before the start of exertional symptoms. This makes identifying exercise-induced dyspnea more important since it helps identify patients whose condition may be changed by early intervention. Additionally, the requirement for stress-based diagnostic techniques is highlighted by the recurrence of symptoms in spite of intact ejection fraction, which calls into question the conventional reliance on resting echocardiogram (54).

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