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# Expiratory Flow Limitation as a Determinant of Orthopnea in Acute Left Heart Failure

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**OBJECTIVES** To assess the contribution of expiratory flow limitation (FL) in orthopnea during acute left heart failure (LHF).

**BACKGROUND** Orthopnea is typical of acute LHF, but its mechanisms are not completely understood. In other settings, such as chronic obstructive pulmonary disease, dyspnea correlates best with expiratory FL and can, therefore, be interpreted as, in part, the result of a hyperinflation-related increased load to the inspiratory muscles. As airway obstruction is common in acute LHF, postural FL could contribute to orthopnea.

**METHODS** Flow limitation was assessed during quiet breathing by applying a negative pressure at the mouth throughout tidal expiration (negative expiratory pressure [NEP]). Flow limitation was assumed when expiratory flow did not increase during NEP. Twelve patients with acute LHF aged 40–98 years were studied seated and supine and compared with 10 age-matched healthy subjects.

**RESULTS** Compared with controls, patients had rapid shallow breathing with slightly increased minute ventilation and mean inspiratory flow. Breathing pattern was not influenced by posture. Flow limitation was observed in four patients when seated and in nine patients when supine. In seven cases, FL was induced or aggravated by the supine position. This coincided with orthopnea in six cases. Only one out of the five patients without orthopnea had posture dependent FL. Control subjects did not exhibit FL in either position.

**CONCLUSIONS** Expiratory FL appears to be common in patients with acute LHF, particularly so when orthopnea is present. Its postural aggravation could contribute to LHF-related orthopnea. (J Am Coll Cardiol 2000;35:690–700) © 2000 by the American College of Cardiology

Orthopnea is a clinical hallmark of left heart failure (LHF), but its mechanisms are poorly understood (1). Orthopnea is also present in various respiratory disorders, for example asthma or chronic obstructive pulmonary disease (COPD). These diseases are characterized by airway obstruction, defined as a reduction in expiratory flow rates. As the disease progresses, the maximal expiratory flow-volume curve becomes increasingly convex toward the volume axis (Fig. 1). When the reduction of expiratory flow rates is sufficiently severe, flow limitation (FL) may occur during tidal breathing, i.e., tidal exhalation lies on or above the forced expiratory flow-volume relationship (2–5, Fig. 1). Flow limitation hinders lung emptying and leads to dynamic hyperinflation, a situation where the end-expiratory lung volume exceeds the elastic equilibrium or relaxation volume of the respiratory system. At this volume, alveolar pressure is equal to atmospheric pressure. With dynamic hyperinflation, the persistent elastic recoil force present at the end of expiration exerts a positive end-expiratory alveolar pressure (intrinsic positive end-expiratory pressure). This pressure must be overcome by the inspiratory muscles before they can generate gas flow toward the alveoli; hence, it represents an inspiratory elastic threshold load. Hyperinflation thus increases the burden on the respiratory muscles by increasing the elastic component of the work of breathing, while the concomitant changes in rib cage geometry put the inspiratory muscles at a mechanical disadvantage (6). This is considered to be a major source of dyspnea. In a recent study

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**Abbreviations and Acronyms**

| | | |
|---|---|---|
| cFL | = | complete flow limitation, or completely flow limited |
| COPD | = | chronic obstructive pulmonary disease |
| EF | = | ejection fraction |
| FL | = | flow limitation |
| LHF | = | left heart failure |
| LV | = | left ventricular |
| NEP | = | negative expiratory pressure |
| nFL | = | not flow limited, or absence of flow limitation |
| pFL | = | partial flow limitation, or partially flow limited |
| SpO2 | = | transcutaneous pulsed oxygen saturation |

of 117 COPD patients (4), FL was the respiratory mechanical parameter that correlated best with dyspnea.

Airway obstruction can occur during LHF through various mechanisms and with various degrees of severity (7). Indeed, acute LHF can mimic acute asthma, a circumstance commonly referred to as "cardiac asthma." Pulmonary function studies have demonstrated increased airway resistance or decreased forced expiratory flows in LHF (8). The rapid increase in left end-diastolic pressure observed during anginal syndrome is accompanied by a fall in lung compliance and an increase in airway resistance (9). The existence of dysfunction in small airways in LHF is suggested by an increased closing volume (10) and the development of an abnormal frequency dependence of total pulmonary resistance (11). Studies of respiratory system impedance with the forced oscillation technique have shown that pulmonary congestion is consistently associated with an abnormal frequency dependence of resistance at low frequencies (12) and have suggested that with severe left ventricular failure there is a significant narrowing of the large airways (12). Finally, some patients with LHF, when challenged with methacholine, exhibit nonspecific bronchial hyperresponsiveness (13).

Based on recent advances in the understanding of dyspnea in COPD, this study was carried out to examine the possible role of FL in the pathogenesis of LHF-related orthopnea. For this purpose, expiratory FL was assessed in the sitting and the supine position with the recently introduced "NEP" (negative expiratory pressure) technique (14) in a population of patients with severe acute LHF and in an age-matched control group. The NEP technique can detect FL during tidal breathing without the need for subject cooperation (5).

**Patients and controls.** All patients admitted over a period of eight months to the Intensive Care Units of the Departments of Pneumology and Cardiology of our hospital with presumed severe acute LHF were screened for inclusion. Inclusion criteria included features compatible with LHF on clinical history, clinical examination, chest X-ray [pulmonary edema was quantitated according to the score proposed by Milne and Pistolesi (48).], blood gas analysis and echocardiographic assessment of left heart function (Table 1). Patients were not included if they were heavy smokers or past smokers (cumulative tobacco consumption above 15 pack-years or tobacco cessation for less than 20 years), had a history of chronic respiratory disease or if clinical examination (14), chest X-ray or blood gases were indicative of COPD. The need for mechanical ventilation was not an exclusion criteria if the patient could be studied while spontaneously breathing through the endotracheal tube.

Twelve patients (7 men, 5 women, age 78 ± 15, height 167 ± 10 cm, weight 66.9 ± 9.8 kg) were consecutively

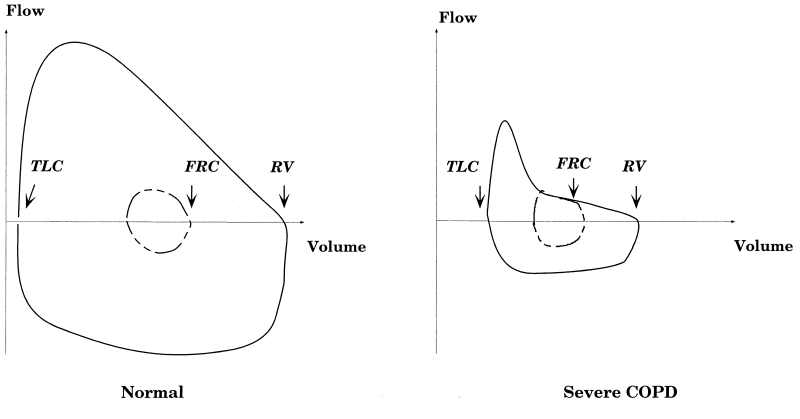


**Figure 1.** Schematic representation of flow-volume curves in a normal subject **(left)** and in a patient with severe chronic obstructive pulmonary disease (COPD) **(right).** The **outermost curves** correspond to a forced maneuver, the **innermost curves** to tidal breathing. In the normal subject, the maximal expiratory envelope is way above the tidal one. In the COPD patient, maximal expiratory flows are reduced at all lung volumes and dramatically so at low lung volumes. Tidal expiratory flow reaches the maximal expiratory flow, defining flow limitation. As compared with normal subjects, residual volume (RV) and functional residual capacity (FRC) are shifted toward total lung capacity (TLC), defining hyperinflation: RV in the patient approximately corresponds to FRC in the normal subject. COPD = chronic obstructive pulmonary disease; FRC = functional residual capacity; TLC = total lung capacity; RV = residual volume.

**Table 1.** Patients Characteristics and Severity of Left Heart Failure

| | Characteristics | | | | Underlying Cardiopathy | | Diagnosis and Severity of Episode of Acute Left Heart Failure | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients | Gender | Age | Weight (kg) | Height (cm) | Nature* | Severity** | EF (%) | RF (breaths/min) | Chest Sounds | Edema on Chest X-ray† | pH | $PaCO_2$ (mm Hg) | $PaO_2/FiO_2$‡ (mm Hg) | Orthopnea | Treatment | Short-Term Outcome# |
| 1 | F | 77 | 52 | 159 | H & Is | 3 | 21 | 38 | C | moderate, alveolar | 7.44 | 34 | 128 | yes | D,N | died |
| 2 | F | 86 | 70 | 165 | H | 3 | 55 | 28 | C, W | severe, alveolar | 7.38 | 45 | 250 | yes | D,N | died |
| 3 | M | 84 | 71 | 180 | Is | 2 | 34 | 27 | C | moderate, interstitial | 7.42 | 36 | 380 | yes | D,N,I | alive |
| 4 | M | 61 | 81 | 171 | Is | 2 | 38 | 21 | C | moderate, alveolar | 7.34 | 43 | 165 | No | D,N | alive |
| 5 | F | 84 | 60 | 155 | Is | 3 | 26 | 28 | C | severe, alveolar | 7.42 | 41 | 170 | yes | D,I | died |
| 6 | M | 83 | 81 | 180 | H | 2 | 24 | 29 | C | severe, alveolar | — | — | — | yes | D,N | alive |
| 7 | M | 83 | 70 | 175 | Is | 2 | 20 | 22 | C | severe, alveolar | 7.40 | 39 | 315 | No | D,N,I | alive |
| 8 | M | 81 | 69 | 173 | Is | 3 | 40 | 30 | C | mild, alveolar | 7.41 | 41 | 305 | yes | D,N | died |
| 9 | F | 80 | 62 | 162 | ? | 3 | 28 | 22 | C | moderate, interstitial | 7.39 | 41 | 290 | No | D,N | alive |
| 10 | F | 98 | 53 | 150 | AS | 3 | 26 | 33 | C, W | moderate, alveolar | 7.48 | 37 | 150 | yes | D | died |
| 11 | F | 79 | 75 | 160 | AS | 3 | 35 | 31 | C | severe, interstitial | 7.44 | 32 | 197 | yes | D,N,A | alive |
| 12 | F | 40 | 59 | 179 | ? | 2 | 18 | 49 | C | severe, alveolar | 7.39 | 39 | 275 | No | D,N,A | alive |

*See Appendix 1 for more details; **NYHA functional class before acute left heart failure; †quantitation of pressure pulmonary edema according to Milne and Pistolesi (48); ‡$FiO_2$ calculated from the measured minute ventilation and the flow of supplemental oxygen received by the patient; #evaluated 1 month after hospital admission.

A = angiotensin conversion enzyme inhibitor; AS = aortic stenosis; C = crackles; D = diuretics; EF = ejection fraction; H = hypertensive; I = inotropic drug; Is = ischemic; RF = respiratory frequency (in breaths/min); W = wheezes.

enrolled (Table 1, Appendix 1). At the time of the study, which took place within the first 24 h after admission in all cases but two (Patients #2 and #8 were studied seven and 10 days after admission, respectively), all patients were treated with oxygen and diuretics. Other treatments are listed in Table 1. All patients but one (Patient #12) had a longstanding history of cardiac disease. Before the acute LHF episode, all patients met the criteria for functional class II or III of the New York Heart Association classification. During the acute episode, their functional impairment corresponded to class IV. The suspected etiology of acute LHF was poorly controlled hypertension in four cases (Patients #1, #2, #4, #11), unstable angina in three cases (Patients #5, #6, #7) and supraventricular arrhythmia in one case (Patient #8). No clear causative mechanism was identified in four cases (Patients #3, #7, #10, #12). To rule out associated COPD, which could have been a confounding factor, the patients' charts were carefully reviewed and the patients were reexamined after the acute LHF episode. In no case did the clinical history or physical findings suggest COPD (14,15). Among patients who survived the acute episode, only two were both fit and cooperative enough to undergo spirometric evaluation (Patients #1 and #4). In these two cases, vital capacity was 91% and 102% of predicted values, with no spirometric signs of airway obstruction.

Ten age-matched normal volunteers, free of chronic cardiac or respiratory disease, served as controls (six men, four women, age 76.7 ± 8.8, 167 ± 10 cm, 70.1 ± 11.7 kg).

The study was conducted according to local ethical and legal rules. The patients or next of kin were informed in detail of the procedures by the clinician in charge and gave written consent.

## METHODS

**Physiological parameters.** Patients were studied while breathing spontaneously (through a size 7.5 endotracheal tube for two of them who had been intubated and mechanically ventilated in the emergency room because of profound hypoxemia and compromised neurological function). Airflow was measured with a pneumotachograph (HR 4700A; Hans-Rudolph, Kansas City, Kansas; linearity: ± 2.6 $L \cdot s^{-1}$) in series either with a rubber mouthpiece (10 patients and 10 controls) or with the tracheal tube (two patients) and connected to a differential pressure transducer (MP 45, ± 2 $cmH_20$; Validyne; Northridge, California). Volume was obtained by integration of the flow signal. Pressure was measured at the mouth or at the airway opening (intubated patients) using a noncompliant polyethylene tubing of 1.6 mm internal diameter, connected to a differential pressure transducer (Validyne DP 15, ± 100 $cmH_2O$). Calibration of all signals was performed at the beginning and end of each session.

**Orthopnea.** The presence of orthopnea was assessed as follows. While the patients were being seated, a semiquantitative evaluation of their perceived "difficulty in breathing"

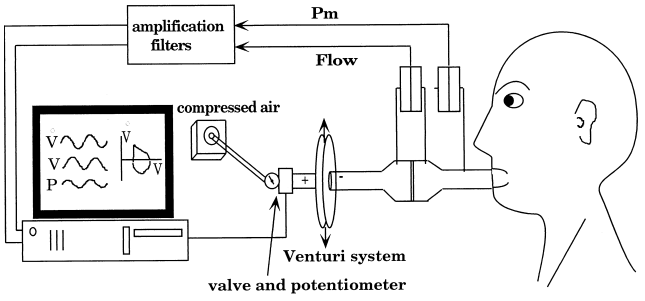


**Figure 2.** Schematic representation of the experimental setup used. A Venturi system is placed in series with a pneumotachograph and a mouthpiece, allowing measurement of flow, volume and mouth pressure (Pm), respectively. When compressed air is fed through the Venturi via a computer-driven valve, a negative pressure is generated at the mouth. Its value can be adjusted using a potentiometer. Signals are conditioned, monitored and stored on a personal computer. Volume is obtained by numerical integration of the flow signal. Pm = mouth pressure.

was first performed using a modified Borg Scale (1) (Appendix 2). After the shift to the supine position, the patients were first asked if they felt better, the same or worse. If they answered "worse," they were presented with the scale again for reevaluation. Orthopnea was arbitrarily defined as onset or worsening of dyspnea when shifting from the sitting to the supine position. This assessment was carried out by an investigator different from the one performing the physiological measurements.

**NEP. APPARATUS.** A negative pressure was applied at the mouth or airway opening throughout tidal expiration, as follows. A Venturi device was placed in series with a pneumotachograph (Aeromech Devices Ltd; Almonte, Canada) (Fig. 2). When fed with compressed air, this device created a negative pressure in the circuit, the magnitude of which could be precisely regulated. The Venturi was connected to a solenoid valve (Asco electrical valve, model 8262G208; Ascoelectric, Canada), which was controlled by a computer and automatically activated when the expiratory flow reached a preset value. The dead space of the equipment was 35 ml. Negative expiratory pressure ($-3.5$ cm$H_2O$) was applied 0.2 s after the onset of expiration and maintained throughout expiration at a level of $-3.5$ cm$H_2O$. A NEP test was performed every five respiratory cycles.

**ANALYSIS.** The response to NEP was analyzed in terms of expiratory flow. In the absence of FL, NEP results in an increase of expiratory flow and a decrease in end-expiratory lung volume (Fig. 3). Conversely, if FL is present, the expiratory flow is unaffected by NEP (Fig. 3) (5,16). [Flow limitation is a term often used to indicate that, in a given patient, the expiratory flows during a forced expiratory maneuver are reduced below the predicted normal. In this study, the term is used to indicate that the expiratory flow rates achieved during the entire, or part, of the tidal expiration are the maximum achievable under the prevailing conditions.]

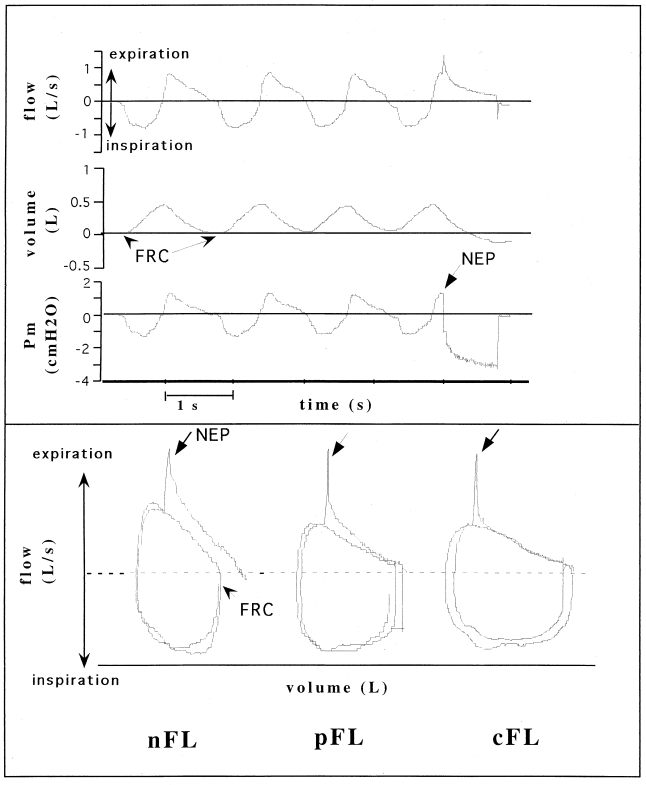


**Figure 3. Top panel:** Flow **(top trace),** volume **(middle trace)** and mouth pressure (Pm, **bottom trace**) vs. time. Negative expiratory pressure (NEP) is applied during the last expiration shown **(Pm trace).** The ensuing expiratory flow is not different from that observed during the preceding control expiration, defining flow limitation (FL). **Bottom panel:** Examples of flow-volume curves in response to NEP **(arrows)** with corresponding curves of preceding control breaths. In the patient without FL (nFL, **left**), the expiratory flow-volume curve with NEP is above that of the control breathing cycle throughout expiration. In the patient with partial FL (pFL, **middle**), the expiratory flow-volume curve with NEP is superimposed on the latter part of the corresponding control expiratory flow-volume curve. In the patient with complete FL (cFL, **right**), the expiratory flow-volume curve with NEP is superimposed on the whole control curve, except for an initial transient increase in flow. See text for further details. cFL = completely flow limited; FRC = functional residual capacity; NEP = negative expiratory pressure; nFL = not flow limited; pFL = partially flow limited; Pm = mouth pressure.

**PROCEDURES.** The patients were first connected to the experimental setup and received supplemental oxygen. Immediately before data acquisition, oxygen was stopped and a nose clip applied. Since the patients were breathing room air during the measurements period, transcutaneous oxymetry ($SpO_2$) was closely monitored. If $SpO_2$ dropped below 94%, the tests were stopped and the patient was back on oxygen. Each run lasted less than 60 s, and interruption because of low $SpO_2$ was seldom necessary.

In all patients and controls, four to six NEP tests and

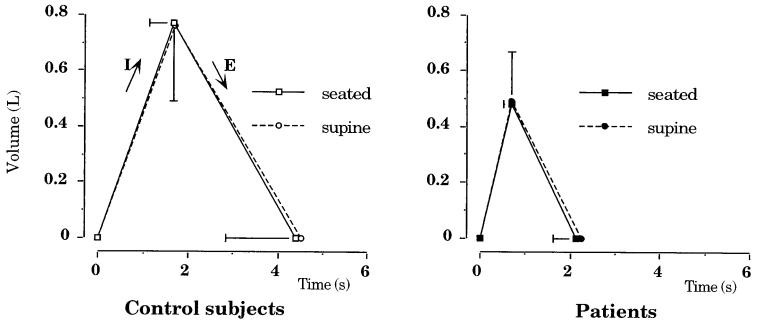


**Figure 4.** Average breathing cycle in the seated **(solid lines)** and the supine **(dashed lines)** position, in control subjects **(left panel)** and patients with acute left heart failure **(right panel).** Bars represent one standard deviation (maximal standard deviation noted in each group at each point). Between groups, differences are statistically significant, whereas between positions, they are not. E = expiration; I = inspiration.

evaluations of dyspnea were performed in each of the following conditions: 1) seated, 2) supine, first 2 min, 3) supine, 15 min or at the limit of clinical tolerance. In four patients, the measurements were repeated after returning to the sitting position. Follow-up studies were conducted in two patients several days later to examine the effects of treatment.

Changes in functional residual capacity between the sitting and the supine position were assessed by comparing the corresponding inspiratory capacities. This was carried out in all controls and attempted in all patients. Due to the severity of the acute respiratory distress, reliable inspiratory capacity maneuvers could be obtained in only four patients.

*Data processing.* Flow and pressure signals were amplified, filtered and then digitized at 200 Hz using a 16 bit analog-to-digital converter (DIREC Physiologic Recording System; Raytech Instruments, Vancouver, Canada) and an IBM-compatible personal computer. All signals were sampled at 200 Hz. The signals were monitored on-line and stored on a hard disk for off-line analysis (ANADAT 5.2, RHT-InfoDat Inc., Montreal, Canada). Negative expiratory pressure cycles suggestive of complete upper airway collapse were discarded (17). Three categories of response were defined (Fig. 3): 1) absence of FL (nFL): expiratory flow increased throughout expiration; 2) complete FL (cFL): NEP did not increase expiratory flow, except for a short initial peak which corresponds to air being suddenly sucked out of the compliant upper airways (cheeks, etc.) and to a small artefact due to the common mode rejection ratio of the flow transducer (5,16); 3) partial FL (pFL): flow increased during the first part of expiration only.

**Statistical analysis.** Within and between groups, comparisons of continuous variables were performed using analysis of variance for repeated measures and a protected least square Fisher's test. Flow limitation being taken as a dichotomous variable, a chi-square test was performed to compare patients and controls and orthopneic versus nonorthopneic patients. Differences were considered significant for a p value less than 0.05. Data are expressed as mean ± SD.

## RESULTS

The two groups were not statistically different regarding age, gender, height or weight.

**Breathing pattern.** In the sitting position, respiratory frequency was significantly higher in patients than in controls (29.3 ± 5.9 vs. 15.4 ± 5.1 breaths/min, p = 0.0001). This was associated with a slightly increased minute ventilation (14.3 ± 6.0 vs. 11.1 ± 3.2 $L \cdot min^{-1}$, p = 0.04) despite a lower tidal volume (483 ± 174 vs. 770 ± 281 ml, p = 0.0002) (Fig. 4). Expiratory time was shorter in patients than in controls (1.43 ± 0.35 vs. 2.63 ± 0.92 s; p = 0.0001). This reduction was proportionally more important than the reduction in tidal volume and in the total respiratory time; hence, in the patients there was slightly increased mean expiratory flow (ratio of tidal volume to expiratory time) (0.366 ± 0.204 vs. 0.305 ± 0.089 $L \cdot s^{-1}$, p = 0.049) and an increased expiratory-to-total time ratio (0.662 ± 0.094 vs. 0.615 ± 0.053, p = 0.0001). The mean inspiratory flow (ratio of tidal volume to inspiratory time), which is an index of inspiratory drive, was higher in patients than in controls (0.715 ± 0.199 vs. 0.473 ± 0.137 $L \cdot s^{-1}$; p = 0.0001).

Shifting from sitting to supine position did not significantly modify the breathing pattern in either the patients or the controls (p = 0.47) (Fig. 4). Since inspiratory capacity decreased by 657 ± 408 ml in controls, functional residual capacity declined in the supine position. This was not the case in the four patients in whom inspiratory capacity could be measured in both positions.

**FL and position.** All control subjects were nFL both sitting and supine. When sitting, eight patients were nFL, three were pFL and one was cFL. Five of the eight patients who were nFL sitting became partially (n = 3) or completely (n = 2) flow limited in the supine position. Two of

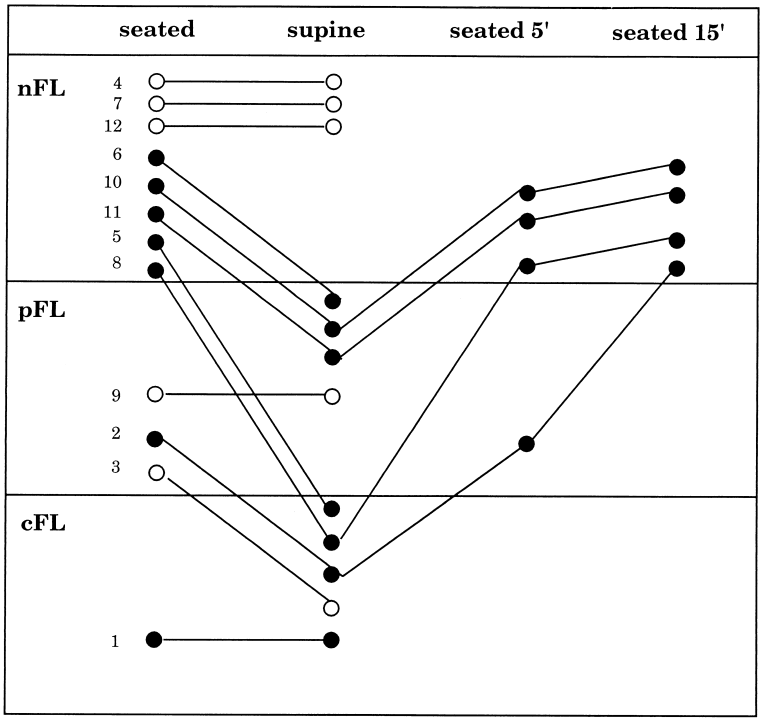


**Figure 5.** Effects of changing position on flow limitation (FL) and orthopnea. Each patient is represented by a number and a symbol placed in the compartment corresponding to his degree of FL. **Closed symbols** represent the patients reporting orthopnea, while **open symbols** correspond to patients without orthopnea. cFL = completely flow limited; nFL = not flow limited; pFL = partially flow limited.

the three patients who were pFL when sitting became cFL in the supine position. Thus, FL either appeared or became more pronounced in the supine position in seven out of nine patients (Fig. 5). It should be noted that the three patients who were nFL both seated and supine (Patients #4, #7, #12) were studied several hours after initiation of treatment with diuretics and vasodilators. Flow limitation was significantly more frequent in patients than in controls both in the sitting ($p = 0.043$) and the supine ($p = 0.003$) position.

Within 15 min of returning to the seated position, the degree of FL had reverted to the initial value in the four patients tested (Patients #2, #8, #10, and #11; Fig. 5). The time course of FL upon changing position was variable, but in most cases it took several minutes for FL to appear to disappear (Fig. 6). In some instances, FL was less when the patient had returned for a while to the sitting position than under baseline conditions (Fig. 6).

In Patients #6 and #11 (initially pFL in the supine position) who were restudied after several days, orthopnea and FL were absent both sitting and supine.

**FL and orthopnea.** Neither the control subjects nor the three patients who were nFL in both seated and supine positions reported orthopnea (Fig. 5). In contrast, the five patients who were nFL when seated but pFL or cFL when supine did. This was also the case of one of the two patients who were pFL when seated and became cFL when supine. Orthopnea occurred significantly more frequently in patients flow limited in the supine position than in not flow limited ($p = 0.003$).

## DISCUSSION

The salient feature of this study is the observation of expiratory FL in supine patients with acute LHF and without evidence of underlying obstructive airway disease. The aggravation of FL in the supine position suggests a possible mechanism for acute LHF-related orthopnea. Before discussing these findings in detail, a brief description of the NEP technique as a tool to detect FL is required.

**Detection of FL.** Flow limitation implies that tidal expiration takes place on or above the maximum expiratory flow-volume curve (3). It is present at rest in most patients with severe airway obstruction although difficult to demonstrate. Indeed, its conventional detection is complex and time consuming. It requires the use of a body plethysmograph (18) and, thus, is neither feasible nor reliable in patients with acute respiratory failure. In addition, the magnitude of the flow during forced expiration depends markedly on the volume and time history of the inspiration that immediately precedes it (19,20). Since, by definition, volume and time history are radically different during resting breathing and forced maneuvers, comparisons of tidal and maximal flow-volume curves may lead to an erroneous assessment of FL (5,21). To overcome these

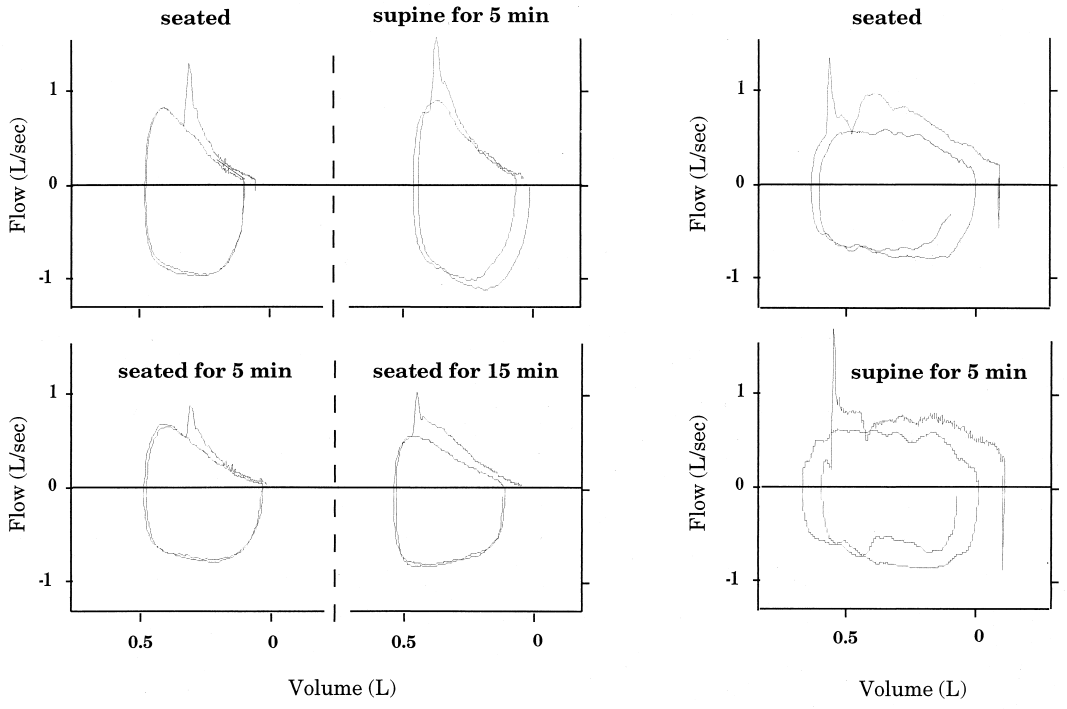


**Figure 6.** Time course of the effect of postural changes on the response to negative expiratory pressure (NEP). Four left panels, in a representative patient (#2); two right panels, in a control subject. In the patient when first studied seated, flow limitation (FL) encompasses less than 50% of tidal volume (pFL; **top panel, left**). Flow limitation worsens (more than 50% of tidal volume, cFL) in supine position (**top panel, right**) and diminishes when the patient returns to the sitting position **(bottom panels).** The degree of FL continues to decrease for several minutes after resuming the sitting position, and after 15 min, the patient is no longer flow limited. In the control subject, there is no FL.

technical and conceptual difficulties, Valta et al. (16) and Koulouris et al. (5) have recently proposed a very simple technique that can detect FL without resorting to forced maneuvers. With this technique, a NEP is applied at the airway opening during a single tidal expiration (Fig. 2), and the ensuing flow-volume curve is compared with that of the previous control expiration (Fig. 3). If NEP produces a sustained increase in expiratory flow, there is no FL. By contrast, if the expiratory flow does not change with NEP, or if the change is only transient (gas decompression from the expiratory line [5,16]), FL is present. Since NEP does not elicit changes in respiratory muscles activity (22), an active resistance to expiration (upper airway narrowing or postinspiratory diaphragm activity) cannot be responsible for the lack of change in expiratory flow. This would imply a performance of respiratory muscles in load compensation far beyond the range of described mechanisms (23). In addition to being devoid of many of the drawbacks associated with other methods, the NEP technique can be applied to noncooperative patients during acute respiratory distress and in any position.

**Expiratory FL and LHF.** Pulmonary function tests in LHF typically demonstrate a restrictive ventilatory defect (24), and low and falling vital capacities have been reported as predictors of heart failure in the Framingham study (25). This is interpreted as reflecting an increase in intrathoracic fluid and enlargement of the heart. Bronchial obstruction is also often present in LHF (7,8). Since the early description of bronchial mucosal swelling in LHF (26), several mechanisms have been implicated. These include: a) accumulation of edema and foam (7,27); b) thickening of the bronchial wall by edema and increased vascular volume, particularly of bronchial veins (28); c) peribronchial edema and vascular engorgement of bronchovascular sheaths (29); d) impairment of the radial distending forces exerted on the bronchial wall by lung elastic recoil through a loss of lung volume (30) or hindered transmission of these forces to the bronchial wall; such uncoupling is an important determinant of lung volume related changes in bronchoconstrictor response to methacholine (31); e) increased airway smooth muscle contractility by humoral and neural mechanisms (7). All the above mechanical and nonmechanical factors can produce airway obstruction in LHF and increase the likelihood of abnormal bronchial responses to otherwise trivial stimuli (13).

Our patients had severe LHF (Appendix 1, Table 1). They all had radiographic evidence of pulmonary alveolar or interstitial edema (Table 1). Two patients had wheezes on auscultation. This makes it reasonable to postulate that airway obstruction was present and severe enough for FL to

occur, particularly since the patients had an increased mean expiratory flow (Fig. 4), which promotes FL (6). Predictably, the mean inspiratory flow was also increased, probably reflecting an increase in central respiratory drive.

The causality of LHF in tidal FL in our patients is supported by the observations in Patients #4, #7 and #12 on the one hand and in Patients #6 and #11 on the other hand. The first three patients were nFL both sitting and supine, despite a clear-cut history of LHF and a clinical presentation highly suggestive of pulmonary edema. However, in contrast to the rest of the study population, they were investigated several hours after the start of depletive and vasodilator therapy. It is possible that by the time measurements were made, they had sufficiently improved for FL to have disappeared. Patients #6 and #11 were reevaluated a few days after the onset of the acute episode, after effective treatment and prior to discharge. In both cases, FL, which was present in the supine position during the initial study, was no longer observed.

Underlying COPD, if present in our patients, would have constituted a confounding factor. However, for FL to occur in COPD, the disease must be severe (4). Selection criteria excluded patients with either known COPD or who were at risk for COPD. In addition, careful chart reviews never elicited findings suggestive of COPD. Spirometric evaluation of two patients performed after the LHF episode ruled out significant obstruction in their cases. Furthermore, severe COPD is associated with particular clinical features (14,15), none of which were present either at recruitment or when reexamined after the acute LHF episode. Therefore, we are confident that COPD severe enough to be associated with expiratory FL was not present in our patients. Finally, it should be noted that the absence of FL in all of our control subjects rules out age as a possible confounding factor.

**Influence of posture on FL.** Several mechanisms can be postulated to explain the clear postural nature of FL in our patients (Fig. 5 and 6). The first is a reduction in lung volume in the supine position. In normal subjects, this may amount to up to 1 L (32), but the influence of postural shifts on lung volume is much reduced in patients with severe airway obstruction (28,32) or LHF (33). Moreover, functional residual capacity did not decrease in the supine position in the four LHF patients in whom it could be assessed, whereas a marked reduction was seen in the control group (657 ± 408 ml). A second mechanism that could account for postural changes in FL is a change in breathing pattern (e.g., increased tidal volume or decreased expiratory time) (6). However, in our patients, tidal volume, breathing frequency, inspiratory time, expiratory time and mean expiratory flow were similar sitting and supine (Fig. 4). This finding is not completely unexpected. In normals, the increases in tidal volume and mean inspiratory flow associated with postural changes are of modest amplitude (34). Moreover, when respiration is stimulated by $CO_2$ rebreathing, posture no longer affects breathing pattern (35). The absence of a postural change in breathing pattern in our patients was, thus, probably due to their respiration being already highly stimulated by the mechanical and chemical changes associated with LHF. A third mechanism could account for postural changes in FL. Changing from sitting to the supine position is indeed associated with some degree of lung flooding, with a shift of blood into the thorax and an increase in extravascular lung water (36). This enhances the bronchial response to methacholine in normals (37), aggravates dyspnea and worsens lung function in asthmatics (38) and causes cardiac asthma in patients with LHF (26). The slow dynamics of FL after postural changes (Fig. 6) support the relevance of this mechanism in our patients (39), as does the beneficial effects of treatment (Patients #4, #6, #7, #11, #12).

**Pathogenesis of orthopnea.** The increased venous return to the lung in the supine position in commonly accepted as a critical trigger to orthopnea. Correlations between left ventricular end-diastolic pressure and orthopnea support this contention (40). Several mechanisms have been proposed that can link an increase in central blood volume with orthopnea. First, the resulting augmentation in pulmonary hydrostatic pressure may lead to increased interstitial edema, stimulation of juxtapillary receptors and increased vagal afferentation (41). Second, increased bronchial wall edema in the supine position could also lead to such a parasympathetic activation (42). Third, orthopnea may result from a rapid increase in the load against which the inspiratory muscles must work, a factor known to promote dyspnea (43). The increase in intrathoracic fluid volume should indeed decrease lung compliance (12), making the lungs more difficult to expand. The onset or exacerbation of FL, as observed in most of our patients (Fig. 5 and 6), should also increase the load opposed to inspiratory muscles (see Introduction). Flow limitation leads to dynamic hyperinflation through incomplete lung emptying, with the persistence of an alveolar pressure above atmospheric pressure at the end of expiration (intrinsic positive end expiratory pressure). Such an additional load to inspiratory muscles is capable of causing breathlessness (44) and probably more so if the ability of the inspiratory muscles to cope with a rapidly instituted hyperinflation has been reduced by preexisting abnormalities (45). One should, hence, keep in mind the fact that chronic left heart diseases impair inspiratory muscle function (46).

We do not have evidence of worsened hyperinflation in the supine position in our patients—this would have required the placement of an esophageal and a gastric probe to estimate pleural pressure and expiratory muscle activity—not feasible in patients with so severe a respiratory distress. Nevertheless, our patients had a rapid and shallow breathing pattern, which is typical of diseases with "stiff lung" but is also consistently observed in patients with obstructive airway diseases, particularly so during acute respiratory failure.

In this setting, the shallow respiration is interpreted as an attempt to minimize energy expenditure during a breathing act that has become heavily loaded (47). If there is FL, however, the correspondingly shortened expiration offsets the putative benefits of this strategy because it promotes dynamic hyperinflation (6). Therefore, the conjunction of 1) the rapid shallow breathing pattern (within increased mean expiratory flow), and of 2) the apparition or worsening of FL seems to us a reasonable ground to hypothesize that, in our patients reporting orthopnea, going to the supine position could have been associated with a rapid increase in end-expiratory lung volume and, thus, in inspiratory load.

To sum up, our hypothesis is not that the sensation of "air hunger" that is typical of LHF is primarily due to an increased load imposed on the inspiratory muscles. Dyspnea and orthopnea in LHF have complex and multifactorial determinants. We only submit here that the sudden increase in this load induced by the onset of FL when assuming the supine position can contribute significantly to the worsening of the respiratory discomfort that defines orthopnea.

**Practical implications and perspectives.** We are aware that the relatively limited number of patients and their age constitute limitations to this study, as does the heterogeneity of the underlying cardiac disease and that of the mechanisms of acute LHF. During acute LHF, however, 11 out of 12 patients had predominantly systolic left ventricular dysfunction, whereas only one (Patient #2) exhibited diastolic left ventricular dysfunction according to echocardiographic findings (Appendix 1). Although heterogeneous regarding cardiac abnormalities, our study population was homogeneous regarding clinical presentation, namely severe respiratory distress with evidence of pulmonary edema of cardiac origin. In spite of its limitations, our study does confirms that severe airway obstruction can be associated with acute LHF. It suggests that FL could be an important determinant of orthopnea in a variety of decompensated cardiac diseases.

From a pathophysiological point of view, it is likely that FL is going to be associated with the most severe forms of acute LHF. Whether and to what extent it exists in less severe forms remains to be determined. Correlations between FL and cardiac status based on sequential NEP measurements will be useful, particularly to understand the dynamics of the functional and anatomical improvement of the lung after therapeutic interventions such as diuresis. The disappearance of FL in those of our patients who were studied after aggressive treatment suggests that NEP might also contribute to an improved monitoring of treatments and, therefore, to more precise adjustments.

From a therapeutic point of view, it may be inferred from this study that interventions aiming at reducing airway obstruction, independent of the specific treatment of cardiac failure, could help in rapidly relieving symptoms in acutely ill patients. [Only integration of clinical, radiological and functional parameters will allow an investigator to distinguish small airways obstructive lung disease from heart failure as the cause of FL, but the dynamics of FL with therapy will certainly prove useful in attributing it, a posteriori, to heart failure.] In support of this idea, methoxamine, an apha-1-agonist that limits the magnitude of LHF-related bronchial hyperresponsiveness (13), has been reported to improve the exercise capacity of LHF patients partly by decreasing their degree of exercise dyspnea (49).

## APPENDIX 1.

*Summary of underlying cardiac disease and echocardiographic assessment during acute left heart failure (LHF). (echocardiographic findings listed under "E:")*

**Patient #1:** 77-year-old woman with a long-standing history of hypertension but no clinical history of angina. *E:* anteroseptal akinesia, LV dilation-end-diastolic diameter: 63 mm, severe systolic left ventricular (LV) dysfunction (ejection fraction [EF] 21%).

**Patient #2:** 86-year-old woman with a long history of hypertension, poorly controlled by diuretics. The episode of acute left heart failure (LHF) seemed to be related to rapidly progressing renal failure. *E:* concentric symetric ventricular hypertrophy (interventricular septum and posterior wall thickness: 15 mm and 14 mm, respectively), normal systolic function (EF 55%)

**Patient #3:** 84-year-old man with diabetes and a history of posterolateral infarct 10 years before. *E:* diffuse hypokinesia with moderately depressed systolic LV function (EF 34%).

**Patient #4:** 61-year-old man with hypertension. *E:* concentric symmetric LV hypertrophy (interventricular septum and posterior wall thickness: 14 mm), anteroapical hypokinesia, moderately depressed LV systolic function (EF 38%).

**Patient #5:** 84-year-old woman with a history of myocardial infarction a few years before. *E:* anteroseptal akinesia, no significant LV dilation, severe LV systolic dysfunction, (EF 26%).

**Patient #6:** 83-year-old man with a history of diabetes, hypertension and exertional angina pectoris. *E:* diffuse hypokinesia, severe LV dysfunction (EF 24%).

**Patient #7:** 83-year-old man with a history of hypertension and dyslipidemia. He had suffered posterior myocardial infarction followed by a coronary artery bypass grafting 17 years before. *E:* marked LV dilation (end-diastolic LV diameter: 68 mm), severe LV systolic dysfunction (EF 20%).

**Patient #8:** 81-year-old man with diabetes, hypertension and chronic atrial fibrillation. *E:* moderate LV dilation, moderately severe LV dysfunction (EF 40%). Rapid atrial fibrillation was present.

**Patient #9:** 80-year-old woman with no particular history of disease. *E:* diffuse hypokinesia, LV dilation (end-diastolic

LV diameter: 64 mm) associated with moderate mitral regurgitation, severe LV dysfunction (EF 28%).

**Patient #10:** 98-year-old woman with severe aortic stenosis. *E:* indexed aortic surface: 0.21 $cm^2/m^2$, diffuse LV hypokinesia, severe LV dysfunction (EF 26%).

**Patient #11:** 79-year-old woman with a history of hypertension. *E:* aortic stenosis (indexed aortic surface: 0.40 $cm^2/m^2$) with mild aortic regurgitation, moderately severe LV systolic dysfunction (EF 35%).

**Patient #12:** 40-year-old woman who had received chemotherapy for a mandibular osteosarcoma 15 months before. *E:* diffuse hypokinesia, LV dilation (LV end-diastolic diameter: 64 mm), severe LV systolic dysfunction (EF 18%).

## APPENDIX 2

*Detection of orthopnea using Borg scale*

While in the sitting position, patients were first asked if they had "difficulty in breathing" (in French, "êtes-vous gêné pour respirer"). If they answered yes, they were presented with the scale below and the following explanations and instructions: "This scale is used to express the intensity of the difficulty in breathing that you perceive. Its graduation goes from '0' which corresponds to 'not breathless at all' to '10' which corresponds to the worst difficulty in breathing that you ever experienced. Please indicate what of the intermediate qualifiers corresponds best to your current status." After lying down, the patients were asked if they felt the same, better or worse. If they answered 'worse,' they were asked to repeat their evaluation on the Borg scale, after Mahler (1).

10__maximal
9__extremely severe
8__
7__very severe
6__
5__severe
4__somewhat severe
3__moderate
2__slight
1__very slight
0__nothing at all

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