Pulm.

HEART-LUNG INTERACTIONS IN HEALTH AND DISEASE

Sharon S. Cassidy, M.D.

Department of Internal Medicine

University of Texas Southwestern Medical School

Grand Rounds

February 19, 1987

Heart-lung interactions is a term applied to the complex interplay between the functions of the heart and respiratory systems. This interdependence of respiratory and cardiac function takes place at several different levels: First, is a functional linkage between the respiratory and the cardiovascular systems in the transport of oxygen and carbon dioxide. Second, are reflex and humoral interconnections between the two systems. Third, are mechanical interactions between the heart and respiratory system (the lungs and chest wall) which are elastic structures that are sealed within an expandable thorax. It is to these mechanical interactions that most attention has been focused in recent years, but prior to considering the mechanical interactions, it is appropriate to consider the other ways that the heart and lungs interact.

I. INTERACTION THROUGH THE RESPIRATORY GASES

The principal function of the heart and lungs is that of supporting oxygen delivery to and CO2 removal from the tissues in accordance with metabolic requirements while maintaining arterial blood oxygen and CO2 partial pressures within a narrow range of normal. The respiratory and cardiovascular systems are series-linked in order to accomplish this function over a wide range of metabolic requirements which may increase 30-fold from rest to heavy exercise.

Because of the large normal capacity for oxygen transport by the lungs and heart, the system is seldom stressed except at exercise, and the earliest symptoms of cardiac or respiratory diseases are often seen only during the stress of exercise.

A. Functional linkage between the heart and respiratory system.

Steps in oxygen transport are:

1) Ventilation and distribution of ventilation with respect to perfusion.

2) Diffusion of oxygen into blood.

3) Chemical reaction of oxygen with hemoglobin.

4) Cardiac output of arterial blood.

5) Distribution of blood to tissues and release of oxygen.

The steps for CO2 elimination are the reverse of those for oxygen delivery.

TABLE 1

Functional capacities and potential maximal oxygen transport of each link in the oxygen transport chain at sea level.

	Link in Chain	Functional Capacity in Normal Man (1)	Theoretical O_2 Transport Capacity	Hypothetical VO_2 Maximum
1	Ventilation	200 L/min	0.030 x MVV	6 L O_2/min
2,3	Diffusion and Chemical Reaction	87 $\frac{\text{ml } O_2/\text{min}}{\text{mmHg } O_2 \text{ grad.}}$	0.07 x $D_{L_{O_2}}$	6 L O_2/min
	[for Carbon Monoxide]	35 $\frac{\text{ml CO/min}}{\text{mmHg CO grad.}}$	0.17 x $D_{L_{CO}}$	
4	Cardiac Output	20 L/min	0.16 x C.O.	3.3 L O_2/min*
5	O_2 Extraction (a-v O_2 difference)	75% (16 ml O_2/100 ml)		

* Actual as well as theoretical

The maximal functional capacity of each link can be determined independently. Table 1 lists these measured functional capacities for healthy young men. Table 1 is adapted from data that appear in two chapters (1,2) that summarize data from several sources. The maximum capacity of each step to deliver oxygen without desaturating arterial blood and without causing tissue hypoxia can be estimated from these functional capacities if a level of hemoglobin (15 g/dl) is assumed. Maximum ventilation in these young men was nearly 200 L/min. The maximum capacity to transport oxygen that could be generated by ventilation in these men [given a physiological dead space ratio (VD/VT) of 0.25 and without allowing alveolar PAO2 to fall below 110 mmHg] would be 0.03 times the MVV or approximately 6 L/min. Maximum DLCO was 35 (ml CO/min)/mmHg CO gradient. DLCO (which is the measurement of diffusion that can be obtained in human subjects) can be converted to DLO2 (which is the parameter that relates the diffusion process to transport oxygen) by multiplying by a factor of 2.5. The maximum capacity to transport oxygen that would be allowed by the process of diffusion and chemical reaction with hemoglobin would be 0.065-0.070 times the DLO2 (or 0.17 times DLCO) or approximately 6 L/min in these average men. Their maximum cardiac output was approximately 20 L/min and the maximum oxygen expenditure was 3.3 L/min. According to various applications of the Fick principle,

O2 delivered = C.O. x arterial O2 content;

O2 returned to heart = C.O. x venous O2 content;

O2 utilization = C.O. x (arterial O2 content - venous O2 content);

O2 extraction = (a - vO2 difference)/arterial O2 content)

these normal, average men had an oxygen extraction of 75% or an a - vO2 difference of 16 ml O2/100 ml. Thus, in normal man at sea level, the limit to oxygen transport is the cardiovascular system and its ability to generate a cardiac output and to distribute the blood efficiently to meet the varying oxygen demands of the different organs.

The maximum cardiac output and oxygen consumption are highly responsive to training and to deconditioning. Bed rest in these normal young males reduced the maximum oxygen transported by approximately 33%. Respiratory diseases do not limit maximum oxygen transport until their functional capacities are reduced nearly 40-50%. The functional capacities of the respiratory system do not appear to be influenced by training in normal individuals; however, there is evidence that ventilatory power and perhaps endurance can be trained with breathing maneuvers in patients with diseases of the respiratory system.

When the limits of the capacity of the respiratory system to transport oxygen are exceeded, or when the distribution of regional blood flow is not proportional to regional ventilation, progressive hypoxemia ensues. If the respiratory centers in the central nervous system do not respond appropriately to increased stimulation by CO2 or if the respiratory muscles cannot respond to increased neural output from the central nervous system, hypercarbia will result. These deviations of O2 and CO2 which are caused by disorders of the respiratory system elicit cardiovascular responses which constitute one type of heart-lung interaction.

B. Chemoregulation of the cardiovascular system.

1) Deviations of both O2 and CO2 from normal exert potent control over the cardiovascular system. These responses to deviations in O2 and CO2 are the result of direct depressant action on vascular smooth muscle and the heart (3,4) and stimulatory reflexes that arise from chemoreceptors located throughout the body (5-7). Chemoreceptors are very small organs with rich vascular and neural supply that are sensitive to changes in O2, CO2 and H+. Reductions in O2 and increases in CO2 and H+ will increase their afferent neural discharge. Stimulation of chemoreceptors by hypoxia causes increase in heart rate, contractility, cardiac output, and systemic vascular resistance through classical sympathetic efferent pathways.

2) Deviations in O2 also influence the pulmonary circulation (8). Hypoxia is the most potent physiologic pulmonary arterial vasoconstrictor known. Regional hypoxia in the lung results in regional vasoconstriction that reduces the blood flow of the region to a level that is appropriate for the ventilation. This optimizes the oxygenation of the blood perfusing that region. Generalized hypoxemia or extensive regional hypoxia will cause widespread pulmonary vasoconstriction that will raise the pulmonary arterial (PA) pressure (9) (Fig. 1). The exact mechanisms by which hypoxemia causes pulmonary vasoconstriction are not known, but reflexes are not a likely mechanism. Either a direct effect of hypoxia on pulmonary vascular smooth muscle or an indirect effect caused by hypoxia-induced release of vasoactive substances from pulmonary endothelial cells are considered the likely source of the vasoconstriction. Hypercarbia and acidosis also cause vasoconstriction of the pulmonary artery.

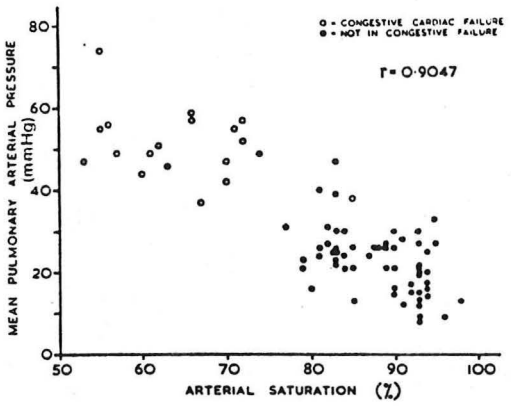

Figure 1 The relation between the mean pulmonary arterial pressure and the arterial oxygen saturation in patients with chronic bronchitis and emphysema. From Heath and Harris, The human pulmonary circulation.

Acute elevations in PA pressure will raise right ventricular (RV) pressures and impair RV function, and chronic elevations of RV afterload leads to RV hypertrophy which further modifies RV pressures, size and function giving rise to mechanical heart-lung interactions.

The integrated cardiac output response that is caused by hypoxia in patients with lung disease is difficult to separate from the cardiac output response of accompanying disorders such as infection, trauma and surgery, shock, etc. However, the cardiac output response to hypoxia can be obtained in normal subjects at high altitude (2) (Fig. 2).

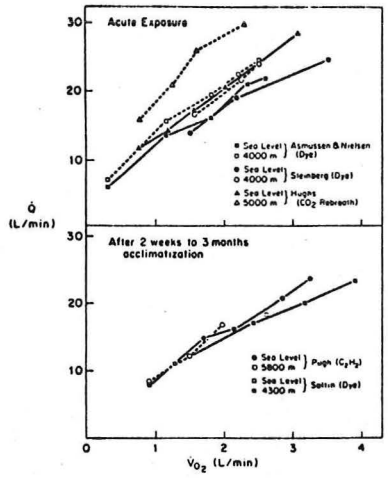

Figure 2 Relationship between cardiac output ($\dot{Q}$) and oxygen consumption ($\dot{V}_{O_2}$) during increasing work loads at sea level and at high altitude. From Johnson RL. Oxygen Transport, In Willerson and Saunders (Eds) Clinical Cardiology, 1977.

The upper panel illustrates the response to exercise in humans during acute exposure to high altitude (open symbols) compared to measurements made at sea level (closed symbols) in three studies. In each study the cardiac output during acute exposure to high altitude (hypoxia) was higher than that measured at sea level (normoxia). The higher the altitude is (5000 m vs. 4000 m), the more severe is the hypoxemia (PAO2 48 mmHg vs. 55 mmHg), and the higher is the cardiac output for any given level of oxygen consumption. Thus, the primary compensatory response to acute hypoxemia is to increase cardiac output. With acclimatization to altitude (hypoxia), the difference in cardiac output between altitude and sea level was lost. Other compensatory measures which increase oxygen transport, such as polycythemia and perhaps shifts in 2-

3 DPG that would optimize the availability of oxygen to tissues, may be responsible for not needing the compensation of an elevated cardiac output to maintain oxygen transport.

C. Chemoregulation of the respiratory system.

The same chemoreceptors whose stimulation by hypoxia, hypercarbia, and H+ ion increases heart rate, ventricular contractility and vascular resistance also feeds back on the ventilatory system and causes an increase in total phrenic motor activity and a shortening of inspiratory time (5,7). This results in an increased respiratory rate and tidal volume which would amplify heart-lung interactions that are mediated by lung volume and/or intrathoracic pressure.

II. NON-RESPIRATORY REFLEX AND HUMORAL HEART-LUNG INTERACTIONS.

The next broad category of heart-lung interactions are those reflex and humoral interactions that do not involve the respiratory gases and are not the result of direct mechanical interaction between the lungs and heart.

A. Non-respiratory lung reflexes.

There are neural reflex pathways between the lungs and the heart that are stimulated either by mechanical distortion of the lung or by exposure of the lung to pharmacological or other chemical substances (not to changes in O2, CO2 or pH). Foremost among these reflexes are lung inflation reflexes (10-14) and the lung chemoreflex (15-17) (not to be confused with chemoreceptors that refer to receptor responsiveness to changes in either O2, CO2 or pH). These reflexes have been quantified in experimental animals where one or both lungs can be isolated and direct mechanical effects of lung distortion on the heart and great vessels and the systemic effects of circulating pharmacologic and chemical compounds can be avoided.

Lung expansion in the resting tidal volume range causes a brief tachycardia that is known as the respiratory arrhythmia (10). The respiratory arrhythmia arises from the same lung afferent system (myelinated nerve fibers) that is responsible for the Hering-Breuer reflex which regulates tidal volume by terminating inspiration when a designated level of lung expansion is attained. Larger expansion of the lungs results in generalized cardiovascular depression with reflex bradycardia, decreases in ventricular contractile state, systemic vasodilation and hypotension (11,12). These reflexes are mediated through afferent nerves that lie in the vagus nerves and through the parasympathetic and sympathetic nervous system by conventional cholinergic and α and β adrenergic mechanisms (12) (Fig. 3). These reflex responses are proportional to the degree of lung expansion between transpulmonary pressures of 10 and 40 cmH2O (14).

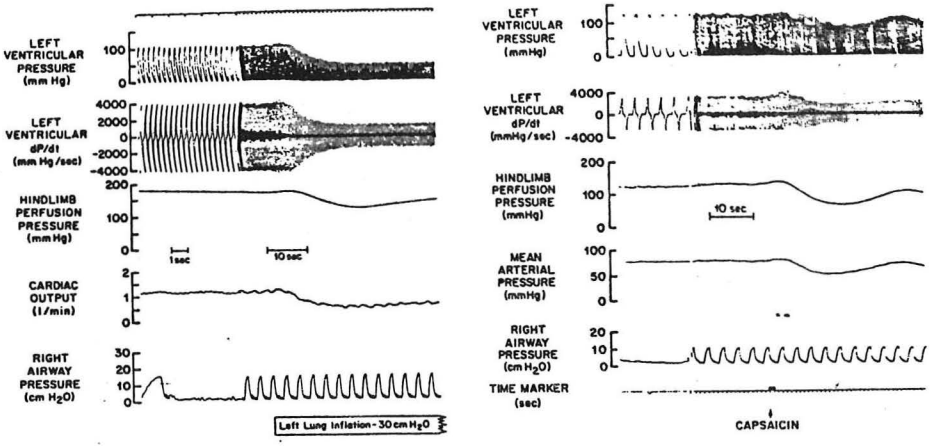

Figure 3 Reflex responses to 30 cmH_2O left lung inflation and to exposure of the left lung to Capsaicin.

The homeostatic purpose that is subserved by this lung expansion cardiodepressor and vasodilator reflex is not known. It is also not known to what degree lung disease might destroy such receptors. It should be considered as a possible mechanism for bradycardia and hypotension occurring with lung hyperexpansion such as in patients with acute asthma or in patients being ventilated at large lung volumes.

The interaction of these reflexes with other homeostatic reflexes such as baroreflexes and the reflexes caused by chemoreceptor activation must be emphasized. An example of these reflex interactions is the heart rate response to chemoreceptor stimulation. If ventilation is not controlled, chemoreceptor stimulation also will cause tachypnea with increased tidal volumes. When tachypnea (which is rendered eucapneic by administering CO2 to the inspired air) is associated with chemoreceptor stimulation, heart rate does not increase. If ventilation is controlled (i.e., no tachypnea response), a brisk tachycardia occurs in response to chemoreceptor stimulation. This absence of a tachycardia in the presence of an otherwise generalized sympathetic response is felt to be due to the offsetting reflex bradycardia that would be caused by the lung expansion. The other sympathetic responses to chemoreceptor activation also are enhanced if the tachypneic response is prevented by controlling ventilation suggesting that the increased lung expansion had limited the full expression of the sympathetic response to chemoreceptor activation.

Exposing the pulmonary circulation to a variety of chemicals and drugs also causes a similar reflex depression of cardiovascular function (13,15-17) (see Fig. 3). In contrast to the hypoxia and hypercarbia induced reflexes, the homeostatic function that is served by these lung chemoreflexes are not known either, but these reflexes might be stimulated by shock or lung injury to cause a non-homeostatic or non-beneficial depression in cardiovascular function.

B. Non-respiratory humoral interactions.

The lung is a very active metabolic organ. Lung expansion, or other mechanical distortion of lung parenchyma, causes release of prostaglandins and perhaps other humoral substances that circulate and are recognized to have potent effects on the systemic as well as pulmonary circulations (18,19). Additionally, pulmonary vascular endothelium is capable of taking up and metabolizing cardiovascularly active compounds (20,21). Endothelial injury such as occurs in the adult respiratory distress syndrome may result in higher circulating levels of substances such as bradykinin because of a reduced capacity to metabolize such hemodynamically potent compounds.

The preceding has been an attempt to survey the areas in which the lungs and heart interact functionally or indirectly and the reader is referred to chapters, rather than to citations of individual studies, in which more detailed information can be gained.

III. MECHANICAL INTERACTION OF HEART AND RESPIRATORY SYSTEM

Mechanical interactions between the heart and lungs are the interactions that have received so much attention recently. In order to assemble a model for understanding mechanical heart-lung interactions, it is necessary to review the basic mechanical functions of the thoracic components: Left and right ventricular mechanics, ventricular interaction, lung and thoracic mechanics, and the mechanics of the cardiac fossa. The cardiac fossa is the name assigned to the space in which the heart rests. The mechanics of this space is coupled to cardiac and respiratory mechanics yet it has a compliance that is separate from them. It is the recognition of this space as a separate thoracic compartment that has been enlightening in the field of mechanical heart-lung interactions. Because the relaxed myocardium is more deformable than the contracted myocardium, mechanical heart-lung interactions will influence diastolic events more than systolic events. Therefore, only the diastolic mechanical properties will be presented. Later, data will be presented verifying the lack of substantial systolic heart-lung interactions except when deviations in intrathoracic pressures are exceedingly large.

A. Left ventricular mechanics.

Diastolic pressure-volume relation of the left ventricle (LV) can be thought of as having three components (23) (Fig. 4).

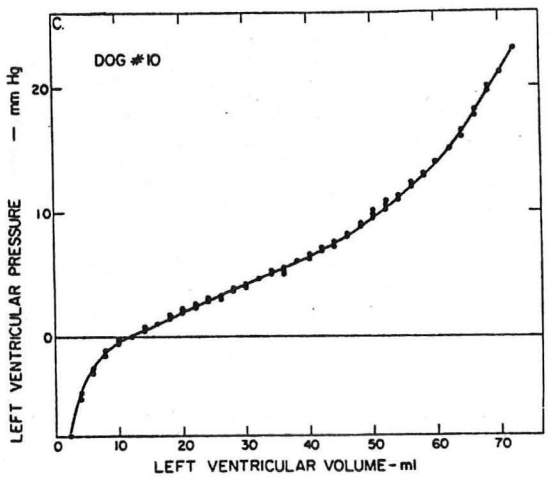

Figure 4 Left ventricular diastolic pressure-volume relations. From Ross, Covill, Sonnenblick, Braunwald, Circ Res 18:149-163, 1966.

At low volumes, the isolated LV empties by collapsing, with little change in pressure, in much the same way as as an unstressed balloon flattens. In the intact chest, the lungs hold the LV walls apart and suction or negative pressure has to be applied to empty the LV cavity. At higher LV volumes, the limits of LV elasticity are reached, and very high pressures are required to expand the LV beyond about 40 ml in this example in a normal dog. Above 40 ml, the LV becomes more stiff. Between 10 and 40 ml, the ventricle is most compliant requiring only 10 mmHg to fill the entire range. Left ventricular diseases that cause LV dilation shift this curve right, and infiltrative myocardial diseases lower LV compliance and shift the diastolic compliance curve up and to the left. When considering an isolated LV preparation, the resistance to expansion is determined by myocardial resistance to deformation. When the heart resides in its normal milieu within the chest, the surrounding structures add to the resistance to LV expansion. These structures are the RV, the pericardium, and the more recently recognized cardiac fossa which includes the lungs and the various components of the chest wall including rib cage, diaphragm, and infra-diaphragmatic structures. When the LV is considered in the context of the surrounding structures, it is referred to as the LV system.

B. Right ventricular mechanics.

The normal RV pressure-volume relation is more flat than the LV (24) (Fig. 5). Within the physiologic range of volumes, the RV is nearly infinitely compliant.

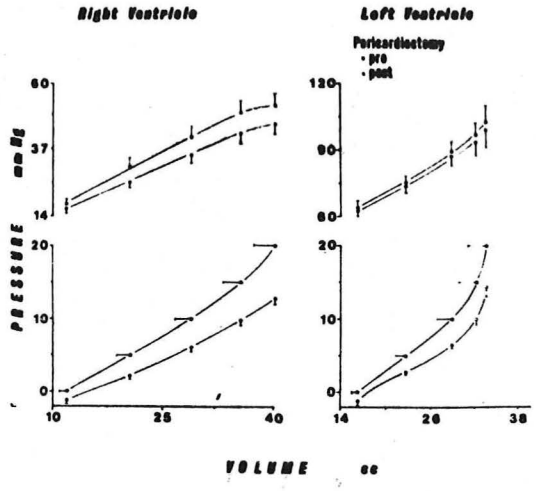

Figure 5. Effects of pericardiectomy on right and left ventricular peak developed (upper half) and end-diastolic (lower half) pressure vs. end-diastolic volume curves. Curves for either ventricle were obtained while end-diastolic pressure in other ventricle was zero. From Janicki and Weber, Am J Physiol 238:H494-503, 1980.

Pulmonary vascular disease and hypertension are frequent companions of many lung diseases, and it is worthwhile to emphasize that elevations in pulmonary arterial pressure dilate the RV. Therefore, the RV may be operating further out on its pressure-volume curve in many instances in which heart-lung interactions are encountered.

C. Ventricular interdependence.

Diastolic pressure-volume relations of either ventricle are dependent on the volume of the opposite ventricle, and the pericardium enhances the degree of diastolic interdependence (24). This interdependence of both ventricles and the added dependence of the pericardium is illustrated in Fig. 6 adapted from Janicki and Weber (24).

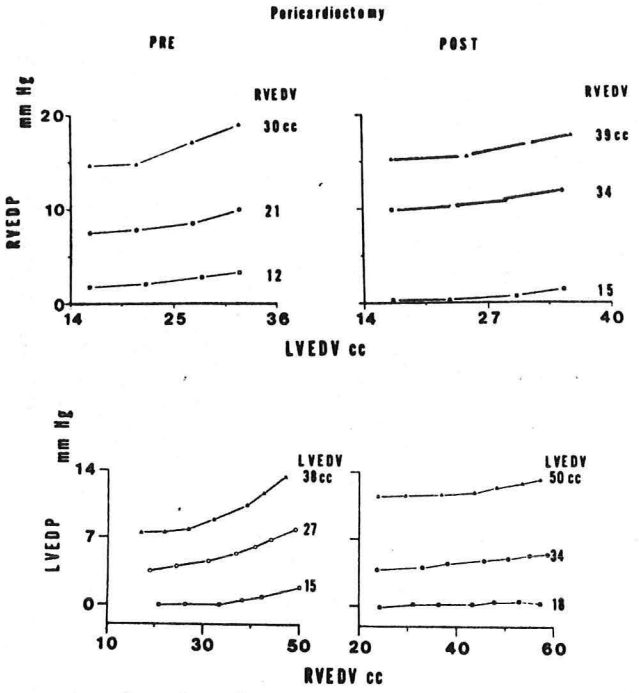

Figure 6. RV and LV diastolic compliance at varying filling of the opposite ventricle. From Janicki and Weber, Am J Physiol 238:H494-H503, 1980.

In the top panel, LV volume is varied while measuring RV pressure. RV pressure rises as LV volume increases indicating a decrease in RV compliance as LV volume increases. This effect is greater if the RV is filled to a large volume compared to a nearly empty RV. The effect is partially, but not entirely, ameliorated by removing the pericardium. Similarly, in the lower panel, LV pressure is measured while filling the RV. The LV, likewise, becomes stiffer as RV volume increases. The effect is more pronounced at larger LV volumes and with the pericardium intact. These hearts are isolated so there are no heart-lung interactions. From these data, we can infer that in situations in which the RV is acutely dilated [i.e., to 50 cc in this example (Fig. 6)], such as occurs with acute pulmonary hypertension, the LV would require 14 mmHg to fill to 38 cc; whereas, it would only require 7 mmHg to fill to that volume without RV dilatation (i.e., RV volume = 30 cc).

Before considering what effect the respiratory system imposes on ventricular mechanics, the mechanics of the respiratory system per se need to be described.

D. Lung and chest wall mechanics.

The lungs and chest wall are lined by a layer of epithelium and a small amount of fluid that permits the opposing surfaces to glide over each other freely. In the relaxed end-expiratory state, elastic recoil of the lungs and chest wall are equal and in opposite directions. These equal but opposing forces are quantitatively reflected in the pressure that exists between the two surfaces which is termed pleural pressure. Measurements of pleural pressure can be estimated from pressure sensing devices placed in the esophagus, and for the purposes of estimating lung and chest wall compliances, pleural pressure and esophageal pressure are considered equivalent. With the exception of a vertical gradient to the pleural pressure which is a function of gravity and lung density, pleural pressure is thought to be uniform

throughout the chest. As a rule, this generalization is valid, especially for assessing compliance of the lungs and chest wall. The exceptions to the uniform distribution of pleural pressure, however, turn out to be very important in understanding heart-lung interactions, and the non-uniform distribution of pleural pressure with respect to the heart surface will be addressed subsequently.

The lungs and chest wall are linked together differently for spontaneously generated inspirations compared to positive pressure inspirations. Spontaneous inspiration is accomplished by action of the respiratory muscles that expand the chest wall (24a). The lungs passively expand by virtue of the sealed thoracic compartment. Pleural pressure falls reflecting the increased recoil of the expanded lung. The degree to which pleural pressure falls, when the lungs are expanded to a designated volume by contraction of the respiratory muscles, is a function of lung compliance and airway and lung resistances. Thus, pleural pressure becomes highly negative during inspiration in patients with stiff lungs, airways disease, or during large tidal volumes.

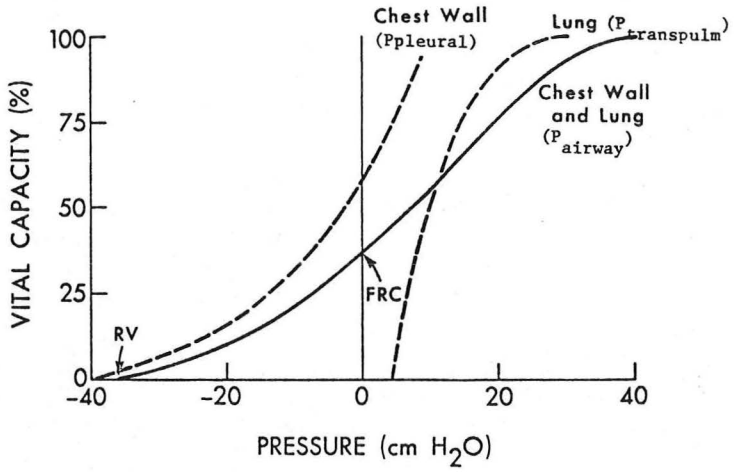

Figure 7 Relaxation volume-pressure relationships of the chest wall (whose pleural pressure is the distending pressure); lung (where transpulmonary pressure is the distending pressure); and the combined lung and chest wall, also called the respiratory system (where airway pressure is the distending pressure). From Agostoni and Mead Handbook of Physiology. Section 3, Respiration, Volume I, 1964.

The determination of pleural pressure during positive pressure lung expansion is entirely different (Fig. 7) (24a). During positive pressure inspiration, the chest wall, as well as the lungs, expand passively. Under these circumstances, the change in pressure across the chest wall is a function of chest wall compliance. When the body is in atmospheric surroundings, this trans-chest wall pressure is simply the pleural pressure. Thus, only the compliance of the chest wall determines the extent to which positive pressure inspiration will increase pleural pressure. The change in transpulmonary pressure is the measure of lung compliance, and the stiffness of the lungs is reflected in a high airway pressure.

For example, a high airway pressure during positive pressure inspiration could reflect only a stiff thorax, such as is seen with thoracic and abdominal trauma and/or surgery, and the compliance of the lungs could be normal. A

high airway pressure also could reflect only stiff lungs with no changes in stiffness of the thorax. Thus, a high inflation airway pressure reflects the presence of a stiff component of the respiratory system, but does not indicate which component may be stiff. However, the issue as to which component may be responsible for a reduced respiratory system compliance that is causing airway pressure to be elevated can be settled by having the patient swallow a pressure sensing device that will rest in the esophagus. A change in esophageal pressure of normal magnitude (approximately 5 cm H2O for a 15 ml/kg tidal volume) with positive pressure inflation would indicate a normal chest wall compliance and presence of a high transpulmonary pressure (i.e., low lung compliance). Likewise, a large change in pleural pressure with positive pressure lung expansion would indicate a stiff chest wall and the presence of a low (i.e., normal) transpulmonary pressure and lung compliance.

Changes in pleural pressure that occur when adding or increasing the end-expiratory pressure are determined by the change in lung volume that is achieved, and this change in lung volume resulting from adding a pressure to the airway is dependent on the compliance of the respiratory system (i.e., both lung and chest wall compliances). For example, if the lungs are fibrosed and very stiff, lung volume will not increase substantially in response to an elevation in end-expiratory pressure; therefore, pleural pressure will not increase substantially.

In summary, the change in pleural pressure during positive pressure tidal volume reflects chest wall stiffness and during spontaneous breathing reflects lung stiffness. These differences are important to keep in mind when considering the consequences of changes in lung mechanics on cardiac filling and emptying.

However, as pointed out earlier, pleural pressure, whether measured between the rib cage and lungs or within the esophagus, is not representative of the entire force being applied to the surface of the heart. This is a recent revelation which will be explored in detail now.

Before we can integrate our understanding of lung and chest wall mechanics with ventricular mechanics and ventricular interdependence, there is one remaining thoracic compartment whose distensibility must be considered. That compartment is the cardiac fossa.

E. Compliance of the cardiac fossa.

One can evaluate the effects of changes in lung mechanics on the cardiac fossa in experimental animals by replacing the heart with a balloon-like device and examining the pressure-volume relationship of the space that the heart would occupy (the cardiac fossa).

Lloyd (25) and Wallis et al. (26) have performed such experiments in dogs. Fig. 8 illustrates their findings. When the fossa was empty, the pressure in the space increased with lung expansion to the same extent that pleural pressure increased. When the fossa was filled, the pressure in the space increased more with lung expansion than did pleural pressure. Thus, with positive pressure lung expansion, the compliance of the fossa was reduced (i.e., the space was less distensible). In other words, this space (the cardiac fossa) has a compliance that is coupled to respiratory system

mechanics via the pleural pressure but not in a 1:1 relationship. For this reason, changes in pleural pressure do not account for all the added resistance to filling of the heart that occurs with positive pressure lung expansion.

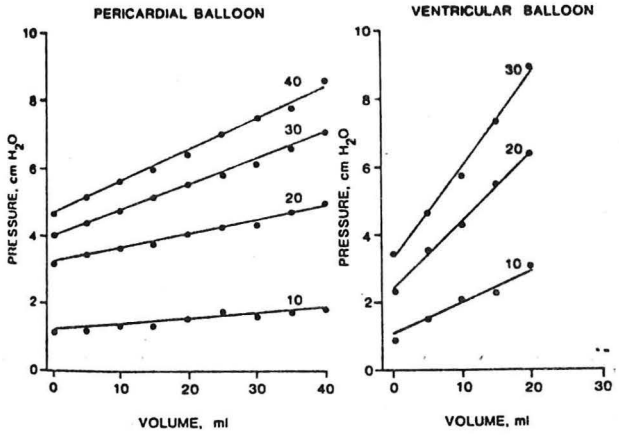

Figure 8 Pressure-volume curves obtained at several end-expiratory pressures with pericardial and left ventricular balloons. End-expiratory pressure (in cm H_2O) is given at right of each curve. From Lloyd TJ, J Appl Physiol 53:57-62, 1982.

There are two possible reasons why the compliance of the fossa would decrease with positive pressure lung expansion. In the first place, lung expansion could decrease the dimensions of the fossa. A smaller space would decrease the effective compliance of the fossa. In addition, increasing the resistance to deformation of the structures that comprise the walls of the fossa also would lower fossa compliance. The right and left lateral surfaces of the heart approximate the mediastinal surface of the lungs. The anterior and posterior mediastinum oppose the anterior and posterior cardiac surfaces. Therefore, we would suppose that factors which stiffen the lung also would lower compliance of the fossa by reducing the distensibility of its lateral walls. Several investigators have shown that during positive pressure breathing, increase in the pressure between the lung and lateral heart surfaces was two to three times as great as the increase in the anterior or posterior cardiac surface pressures (26a,26b).

It is customary to view lung compliance from the airway to pleural surface (i.e., the pressure required to inflate the lung). From the viewpoint of heart-lung interactions, the lung compliance that is in question is the pressure required to deform the regional lung surface (i.e., pleural surface to airway pressure) because the ventricles must deform the lung surface to fill during diastole. Lloyd called this compliance of the respiratory system viewed from the cardiac fossa (25).

The effect of positive pressure inflation on the resistance of the lung surface to deformation has been studied by measuring how far a weighted probe will indent the lung surface (Fig 9) (26c). At low levels of inflation pressure, the probe will indent the surface as much as 14 cm. However, as inflation pressures increase, this depth is reduced until at full expansion the lung is nearly incompressible. Under circumstances in which lung

expansion approaches total lung capacity in subjects whose thoraces are intact, we would envision that the fossa could not be expanded in the lateral direction as easily as in the anteroposterior direction. This potential change in geometry of the fossa, however, has not been examined directly.

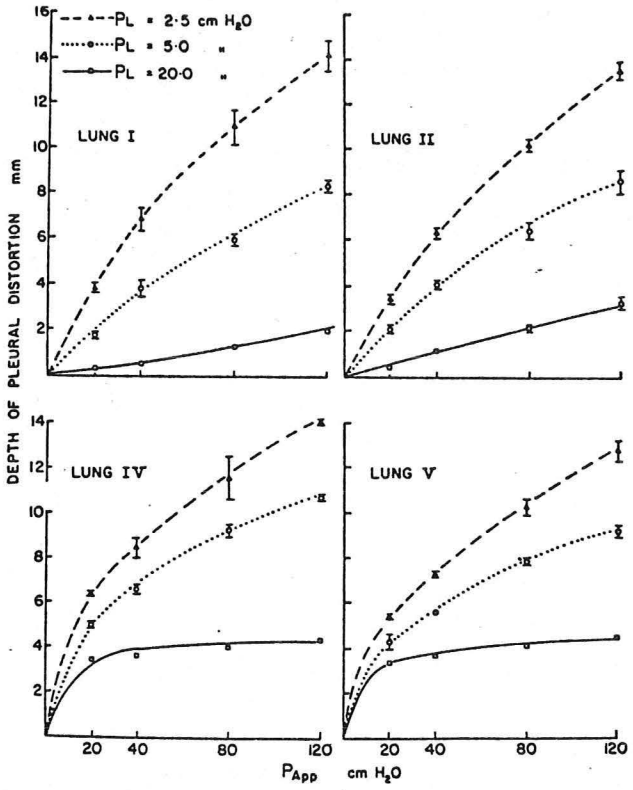

Figure 9 Distortions produced in pleural surface by various localized pressures. From Robertson, Hall and Hogg, J Appl Physiol 34:344-350, 1973.

Therefore, the question is raised as to the interaction between the cardiac fossa and the ventricles. Lloyd and Wallis et al. (25,26) asked this question also by repeating their studies in animals in whom the heart had been replaced and measuring the pressure within the LV cavity as its volume was systematically expanded (Fig 8). LV pressure-volume studies were repeated at varying degrees of positive pressure lung expansion. The LV, like the fossa, became stiffer at higher levels of lung expansion. This increase in pressure required to fill the LV to a large, but not excessive, volume at high airway pressures was much more than the increase in pleural pressure. The decrease in LV compliance with positive pressure lung expansion was greater than the decrease in fossa compliance which suggests that when the fossa is compartmentalized, a single compartment may be less compliant than the whole fossa.

To summarize these findings regarding the cardiac fossa, lung expansion with positive airway pressure reduces the size of the space in which the heart sits and reduces its distensibility far more than can be accounted for by the change in pleural pressure. The stiffness of the fossa adds to the

pericardium and to the volume of the opposing ventricle to decrease the effective compliance of the LV system.

From these data, we can generalize that, concerning previously reported studies of cardiac responses to positive pressure lung expansion, the degree of LV filling cannot be estimated from the measurement of LV end-diastolic pressure (or mean atrial pressure) and pleural pressure alone. Thus, calculating transmural pressures using pleural pressure, regardless of how carefully it is measured, are not meaningful estimates of LV volume because the change in the compliance of the cardiac fossa is not fully reflected in the change in pleural pressure.

Summarizing from this review of thoracic mechanics, there are several phenomena which could render the left ventricular system less compliant that are solely the result of changes in respiratory mechanics. They are:

1) Increased airway pressure.

2) Lung expansion with positive pressure.

3) Reduced compliance of the lung.

4) Reduced compliance of the chest wall.

5) Pulmonary hypertension with RV dilation.

There are three obvious implications of these mechanical heart-lung interactions for clinical medicine.

First is that greater pressures will be required to fill the left ventricle. Marini et al. (27) demonstrated the effect of this decrease in LV system compliance that is caused by positive pressure lung expansion in living dogs by measuring cardiac output at several levels of i.v. volume expansion during two different levels of positive pressure breathing (Fig 10).

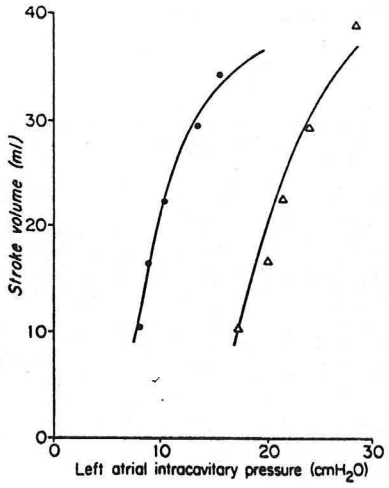

Figure 10 Left ventricular function data before (●) and after (Δ) 15 cm H_2O PEEP. From Marini, Culver, Butler, J Appl Physiol 51:1367-1374,1981.

They generated Frank-Starling function curves at normal lung volumes and under circumstances in which lung volumes and airway pressures were increased by adding a threshold pressure to the expiratory level to prevent the lungs from expiring to their normal resting level. This is usually referred to as PEEP, or positive end-expiratory pressure. They showed that much higher LV pressures were needed with PEEP to attain comparable stroke volumes. These higher end-diastolic pressures occur at the expense of elevating pulmonary capillary pressures. Although some of this increase in pulmonary capillary pressure may be offset by elevations in alveolar pressure, it is not at all clear that the net effect on fluid transudation would be zero. In fact, nearly every study that has examined the effects of ventilation with PEEP on lung fluid balance has shown that PEEP substantially increases accumulation of fluid within the lung (27a).

Another important clinical implication of these heart-lung interactions is that direct or indirect (Wedge pressures) measurements of LV end-diastolic pressure do not reflect the extent of LV filling because of the change in LV system compliance. This alters our interpretation of pulmonary capillary wedge pressures. If the change in compliance of the fossa or the LV system cannot be estimated, the wedge pressure cannot be adjusted to accurately reflect LV end-diastolic volume. Later, a method to potentially estimate the change in LV system compliance that is caused by ventilator-induced heart-lung interactions will be presented. This problem in estimating LV volume when LV compliance is changed is not to be confused with the problems of catheter placement which must be in the lower regions of lung (i.e., Zone iii of the Zones of West) in order to reflect the downstream left atrial or end-diastolic pressure.

A third potential implication of these mechanical heart-lung interactions is that regional ventricular function may be altered by severe distortions of the fossa and by stiffening of its walls. The question of whether systolic function is acutely or chronically impaired has not been adequately examined. Stiffened walls of the fossa may be difficult to deform during systole also, or the stiffened walls may actually assist systole. Furthermore, the potential exists that alteration in regional cardiac surface pressures could redistribute blood flow inappropriately. In addition, regional stress-strain relations may be altered which could have delayed, if not immediate, effects on regional ventricular function. In spite of the frequency with which the question is raised of whether lung disease per se could impair LV function, there is a lack of experimental data that conclusively address this question.

Before leaving the subject of the mechanics of the cardiac fossa, it would have been appropriate to consider the effects of spontaneous breathing on the compliance of the fossa. However, there is nothing known about the effects of spontaneously generated inspiration on the cardiac fossa. The effects could be opposite of positive pressure lung expansion (i.e., the fossa size could become larger and the walls of the fossa could become more distensible). However, the changes could be mixed because while intrathoracic pressures change oppositely, lung volume increases in both, and presently we do not know the effect of spontaneous breathing on the fossa.

IV. APPLIED PHYSIOLOGY OF HEART-LUNG INTERACTIONS

A. In health (normal cardiac and respiratory system mechanics).

1. Spontaneous ventilation.

In individuals with normal lungs and chest walls, the change in respiratory system mechanics that is experienced is inspiration. With exercise, inspiration generates a large change in lung volume and a large fall in pleural pressure. It is not known in what way spontaneously generated lung expansion will alter the size, shape, and compliance of the fossa.

We do know that even a normal inspiration at rest is associated with an increased RV stroke volume and decreased LV stroke volume in man and dog, conscious and anesthetized (28,33). The mechanism of the increased RV output has not been thoroughly investigated because of difficulty in measuring RV volumes throughout a respiratory cycle, but it is believed to be the result of both preload augmentation caused by increasing the gradient for venous return to the RV and afterload reduction caused by a lowering of pulmonary vascular resistance (28). The area of most interest and controversy has been the mechanism(s) responsible for the lowering of LV stroke volume. The reduction in LV stroke volume is the mechanism that is responsible for the inspiratory fall in systemic blood pressure, also known as pulsus paradoxus. The reduction in LV stroke volume during a normal resting inspiration is about 15%. The possible mechanisms for reduced LV stroke volume during inspiration are:

1) Reduced LV preload caused by pulmonary venous pooling of blood.

2) Reduced LV preload due to decreased LV compliance caused by increased RV filling.

3) Increased LV afterload caused by the lowered pleural pressure.

Although it would seem that the diastolic ventricle would be more susceptible to the small changes in intrathoracic pressure and lung volume that occur with resting tidal volume, it has been proposed that the mechanism responsible for the reduction in LV stroke volume during a normal inspiration is actually an increase in LV afterload (29). However, the preponderance of data suggest that the reduction in LV stroke volume is caused by a reduction in LV preload (30,31).

To address some of these issues, we have studied the LV dimensions of dogs throughout the respiratory cycle using biplane cinefluorography of dogs with markers implanted in their hearts. We found that the inspiration-induced fall in LV stroke volume was caused by a reduction in LV preload without significant changes in LV afterload (32) (Fig. 11). The question then arose as to the mechanism responsible for the reduction in LV preload. If the LV behaves homogeneously and blood were pooled in the lung, we would have expected the diastolic LV to have decreased more or less proportionately in all three axial dimensions. However, we observed a noticeable change in diastolic LV shape caused by inspiration. The LV actually widened in the anteroposterior direction, while narrowing from the lateral as well as the septal side. This suggests that during spontaneously generated inspiration there are direct heart-lung interactions involving the LV.

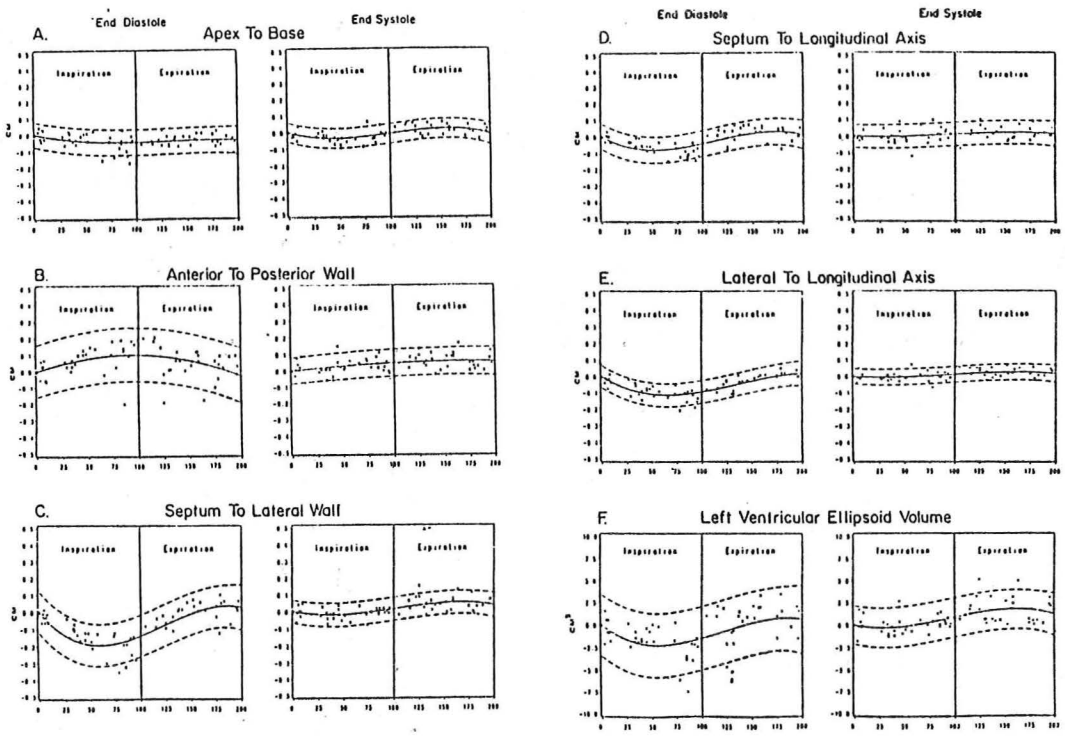

Figure 11 Changes in LV dimensions throughout the respiratory cycle.

However, we do not know if the LV is being compressed from the lateral side, or if the anterior and posterior LV walls are being pulled outward. Thus, we would add to the previous list a fourth possible mechanism to reduce LV stroke volume during inspiration:

4) Decreased LV preload caused by heart-lung interactions that alter the geometry of the LV, and thereby, reduce LV compliance.

It remains to be learned whether increased ventilation will exaggerate these responses and whether increased cardiac output during exercise will ameliorate the mechanical effects of increased tidal volumes.

2. Müller maneuver.

A Müller maneuver is the generation of a maximal inspiratory effort against a closed glottis. Usually a Müller is performed after exhaling maximally to residual lung volume. This maneuver generates intrathoracic pressures of -100 to -150 mmHg without a change in lung volume. A Müller maneuver also increases RV stroke volume and reduces LV stroke volume (33), but not much more is known about the mechanisms other than the potential causes listed for spontaneously generated inspiration.

3. Positive pressure ventilation.

Positive pressure inspiration causes a reduction in both LV and RV stroke volumes (28). RV stroke volume is reduced primarily because of increased gradient for venous return to the RV, but also because RV afterload is increased although to a small degree which would augment the reduction in RV stroke volume. The mechanism responsible for reducing LV stroke volume has not been studied systematically, but is probably the result of decreased LV compliance for all the reasons that have been described by which positive pressure lung expansion reduces LV compliance (25,26). The effects of positive pressure ventilation with added positive end-expired pressure will be presented more thoroughly later.

4. Valsalva maneuver.

A Valsalva maneuver is performed by inspiring to total lung capacity, closing the glottis, and forcibly attempting to expire against the closed glottis for several seconds. Performing a Valsalva maneuver generates intrathoracic pressures of +100 to +120 mmHg. A Valsalva also reduces LV stroke volume and blood pressure (34). Historically, the purpose of performing this maneuver was to test the intactness of the autonomic compensatory response to a fall in blood pressure, presumably caused by a reduction in LV stroke volume.

The mechanisms responsible for the fall in LV stroke volume are not clear, but include positive pressure lung expansion, reflex cardiodepressor and vasodilator response to lung expansion, and reduced venous return to the RV since the maneuver is sustained throughout several heartbeats.

B. Heart-lung interactions caused by respiratory diseases and by controlled mechanical ventilation.

Virtually all that is known about the effects of lung diseases such as emphysema, asthma, pulmonary fibrosis, or pulmonary edema on the heart and circulation has been obtained without our awareness of the cardiac fossa or how reducing its size or stiffening its walls would alter our interpretation of intracardiac and pulmonary arterial and wedge pressures. The problems of having to rely on pressure measurements to estimate ventricular volumes have been overcome to a degree with newer non-invasive cardiovascular techniques such as 2-D echocardiography in which estimates of RV and LV size can be obtained from cross sectional dimensions, and first pass nuclear scintigraphy in which ejection fractions, indicator dilution measurements of cardiac output, end-diastolic and end-systolic volumes are derived. However, these methods have seldom been applied to directly answer questions that are being raised regarding heart-lung interactions. The reluctance to use these techniques to study heart-lung interactions stems from the lack of dynamic quality needed to study serial heartbeats (i.e., gating techniques could not be employed to study heart-lung interactions during inspiration) and from variations in cardiac rotation throughout the respiratory cycle. Nevertheless, what is known about the effects of various types of lung disease on cardiac function will be presented and will be discussed from the perspective of heart-lung interactions.

Lung diseases potentially will alter cardiovascular function by virtue of all the physiological mechanisms outlined earlier. In summary, the potential mechanisms are:

1) Increased RV afterload.

2) Hypoxemia.

3) Hypercarbia and acidosis.

4) Altered intrathoracic pressures.

5) Altered lung volume.

There are three pathophysiological states for which there are substantial data regarding the effects of the lung disorders on cardiovascular function. These are chronic obstructive pulmonary disease (COPD), the adult respiratory distress syndrome (ARDS), and positive pressure ventilation with PEEP. These disorders have been characterized with respect to hemodynamics (cardiac output and ventricular pressures), ventricular function (ejection fractions). The cardiovascular effects of these disorders have been reviewed in detail recently in a symposium on cardiopulmonary interactions (35).

To discuss the cardiovascular effects of COPD, ARDS, and PEEP, it will be necessary to consider systolic function, especially that of the RV, in addition to diastolic function. Lung diseases are often associated with pulmonary hypertension, and the RV does not perform well against an elevated PA pressure. The right ventricle is often referred to as a volume pump rather than a pressure pump, and Fig. 12 illustrates this point. Raising mean PA pressure 20 mmHg above normal reduced RV stroke volume approximately 30%; whereas, a 20 mmHg increase in mean systemic pressure reduced LV stroke less than 5%. Further acute increases in mean PA pressure lead to RV failure. However, increasing RV preload (Fig. 12b) causes very little increase in RV stroke work as compared to the LV whose work greatly increases when preload is increased. Thus, seemingly small elevations in RV afterload (20 mmHg) have a relatively large effect on cardiac output.

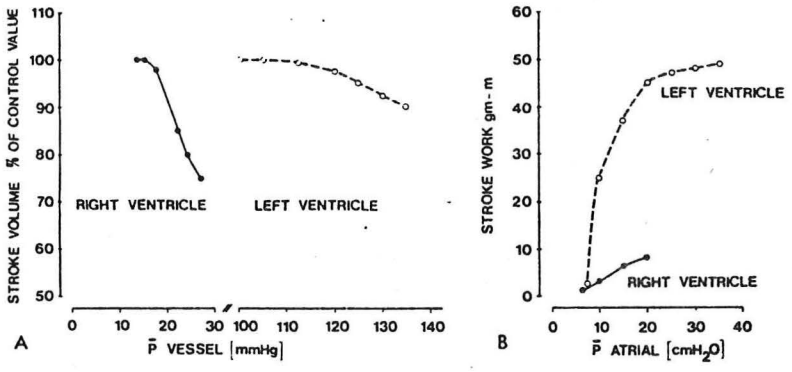

Figure 12 Effects of increasing afterload (A) and preload (B) on the right and left ventricles. From McFadden ER and Braunwald E, In Braunwald (ed): Textbook of Cardiovascular Medicine.

1. COPD

Patients with emphysema, chronic bronchitis, and asthma are grouped together under the term COPD. This is done of necessity because often patients with airway obstruction do not fit into clear categories of emphysema, bronchitis, or asthma. However, this lumping together of these disorders is unfortunate from the viewpoint of being able to determine precise mechanisms that are responsible for derangements in cardiovascular function. These patients have variable degrees of pulmonary hypertension that fortunately do correlate closely with arterial oxygen tension. However, lung volumes vary widely as do pleural pressures, and the effects of altered respiratory system mechanics on the compliances of the LV and RV systems can only be conjectured.

Mild to moderate obstructive lung disease is not associated with any demonstrable alteration in hemodynamics; cardiac output, end-diastolic pressures; pulmonary vascular resistance, pulmonary arterial pressure or in RV or LV ejections fractions at rest (35). Exercise, however, generally causes a mild increase in right sided pressures and RV stroke work compared to normal subjects. When COPD is moderately severe and is associated with hypoxemia, pulmonary hypertension occurs at rest, and is associated with elevated cardiac output (36) (Fig. 13). With exercise, PA pressures may reach 60-80 mmHg, but cardiac output does not rise as would be expected. RV end-diastolic pressures increase markedly, suggesting the RV is operating on the ascending limb of its pressure-volume curve (36).

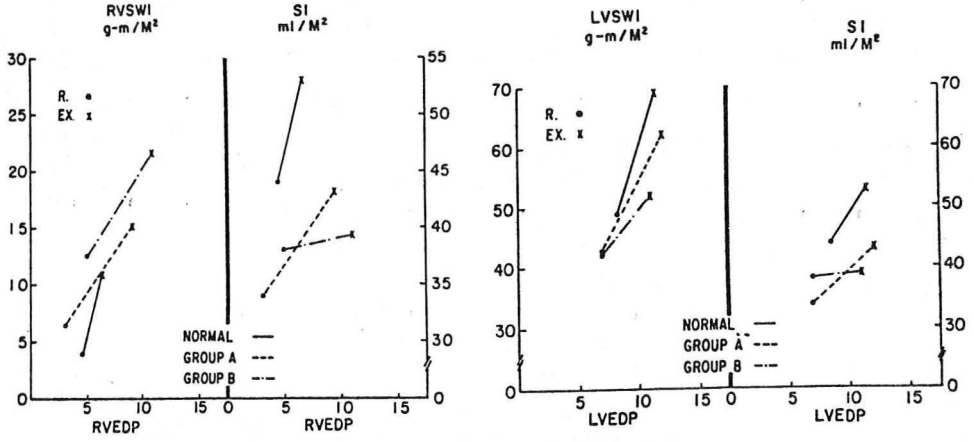

Figure 13 RV and LV stroke work index (SWI) and stroke index (SI) in normals and in patients with COPD without (A) and with (group B) cor pulmonale. From Khaja and Parker Am Heart J 82:319-327, 1971.

RV ejection fraction coorelates well with peak pulmonary arterial systolic pressure (PPASD) (Fig. 14) (35).

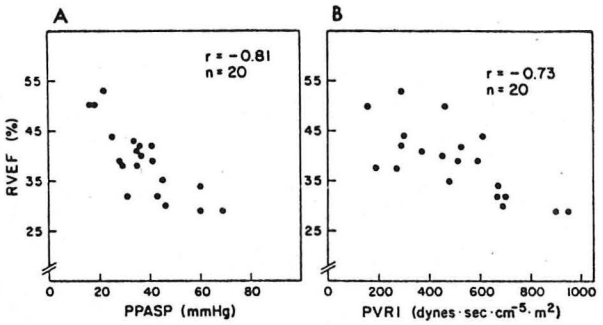

Figure 14 Relation of right ventricular ejection fraction (RVEF) and peak pulmonary arterial systolic pressure (PPASP) in Panel A and pulmonary vascular resistance index (PVRI) in Panel B. From Brent BN, Berger HJ, Matthay RA, et al. Am J Cardiol 50:255-262, 1982.

In a group of patients with COPD without cor pulmonale that were not discriminated with respect to severity of obstruction, RV ejection fractions were slightly below normal 50% vs. 55% at rest, but many (1/3) showed a decrease in RV ejection fraction with exercise (Fig. 15) (37). This suggested that RV ejection fractions measured at rest and during exercise could be used to identify those with occult pulmonary hypertension.

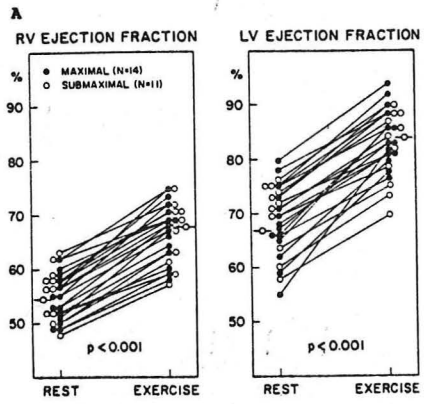

Figure 15a Right ventricular (RV) and left ventricular (LV) ejection fractions at rest and exercise in normal control subjects. From Matthay RA, Berger HJ, Davies R, et al. Ann Intern Med 93:234-239, 1980.

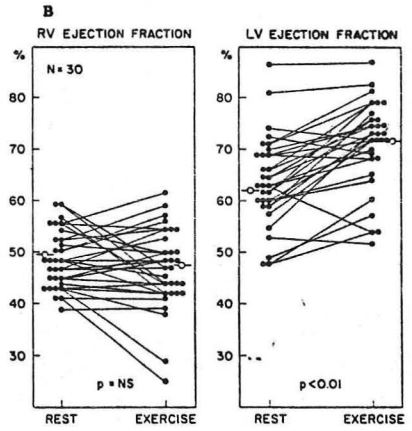

Figure 15b Right ventricular (RV) and left ventricular (LV) ejection fractions at rest and submaximal exercise in 30 patients with COPD. From Matthay RA, Berger HJ, Davies R, et al. Ann Intern Med 93:234-239, 1980.

Left ventricular function in patients with COPD has been a controversial topic for many years. The occurrence of LV dysfunction is not questioned so much as is its etiology.

The potential sources for LV dysfunction include:

1) Hypoxemia and global myocardial ischemia.

2) Ventricular interdependence with reduction in LV compliance.

3) Associated myocardial diseases that afflict the same age group.

4) Heart-lung interactions which reduce LV compliance.

LV end-diastolic pressures often but not always have been reported elevated at cardiac catheterization in patients with COPD (35). An elevated LV end-diastolic pressure does not indicate whether there is myocardial dysfunction, volume overload, or whether compliance of the LV system is reduced. In either case, the implications would be the same regarding the relationship between LV end-diastolic pressure and pulmonary capillary pressure and congestion. However, the implications regarding LV volume and myocardial function would depend on whether LV failure, volume overload, or a reduced LV compliance existed.

Post-mortem studies have shown LV hypertrophy in patients who otherwise had no reason for hypertrophy (i.e., no systemic hypertension) (35). Changes in LV eccentricity caused by heart-lung interactions or ventricular interdependence may alter LV stress-strain relationships which may be a stimulus for hypertrophy. LV ejection fractions are occasionally reduced in patients with COPD, especially during exercise (Fig. 13,15), but these studies lack corroborative data to associate or disassociate reduced LV ejection with end-diastolic pressures or volume. Common therapeutic measures in patients with COPD, such as terbutaline and aminophylline, will improve LV as well as RV ejection fractions. This could be an inotropic effect, or it could be a vasodilator effect with lowered PA and RV pressures, or lung mechanics may be improved and heart-lung interactions lessened. Any combination of the three mechanisms could be responsible for improved ventricular function.

Because of the loss of elastic recoil in emphysema, lung volume is increased and pleural pressures often are higher than normal and may be positive. Inspiration is relatively easy, but expiration is prolonged and forced, creating even higher alveolar pressures. This increased lung volume and high alveolar pressures might be expected to reduce fossa size and increase the stiffness of its walls. However, this is merely speculation because we do not know the effect of emphysema on the cardiac fossa. Similar pathophysiology may occur with asthma, and having patients reduce their expiratory work may improve cardiac filling as well as reduce the wasted metabolic costs of forced expiration.

2. ARDS

The syndrome of acute lung injury occurs in a wide variety of settings. It is recognized by the clinical and radiological findings of pulmonary edema and by the severe hypoxemia that accompanies the lung injury. The alterations in hemodynamics have been documented rather thoroughly by several investigators (35,38). ARDS hemodynamically is characterized by tachycardia, pulmonary hypertension, decreased LV stroke work and stroke index (Fig. 16 and 17) (38,39). Different from COPD is the higher incidence of LV failure or dysfunction occurring in over half the patients in one series (38). Unfortunately, many of these patients do not survive, and autopsies have shown LV myocardial necrosis to be present in a high number (38).

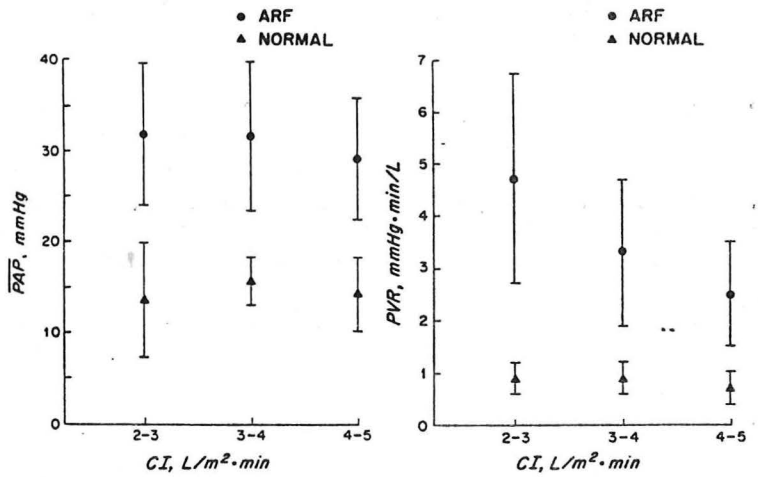

Figure 16 Mean pulmonary artery pressure ($\overline{PAP}$) (A) and pulmonary vascular resistance (PVR) (B) as a function of cardiac index (CI) for patients in acute respiratory failure (ARF) and for normal controls. From Zapol and Snider, N Engl J Med 296:476-480, 1977.

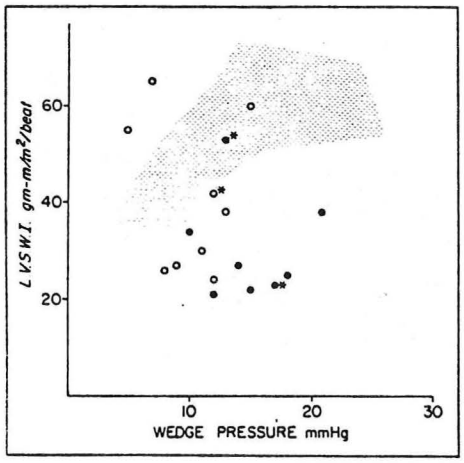

Figure 17 Relationship between wedge pressure and left ventricular stroke work index (LVSWI) in patients with ARDS studied while receiving 0 to 5 cm H_2O of PEEP. (O) indicate data from survivors; (●) indicate data from patients who died; and (*) indicate patients receiving intravenous inotropic agents at the time of study. The shaded area indicates the expected relationship between wedge pressure and left ventricular stroke work index. From Zimmerman, Morris, and Cengiz, Am J Med 73:25-34, 1982.

However, interpretation of post-mortem findings is difficult because these patients terminally have profound hypoxemia. However, the potential causes for the LV dysfunction in ARDS include:

1) Anatomical changes in the myocardium caused by:

   a) hypoxemia induced ischemia;

   b) ARDS associated injurious agents.

2) Reduced compliance of the LV system caused by:

a) RV dilation;

b) heart-lung interactions caused by pulmonary edema;

c) heart-lung interactions caused by PEEP.

Many believe that the reduction in cardiac output and LV performance is because of an interdependence mechanism. Data from Zapol's study would tend to support the interdependence mechanism because decreased cardiac output was tightly correlated with PVR (39). Pulmonary hypertension is often higher than expected from the hypoxemia. Specific pharmacologic vasodilator treatment is often advised; however, the number of patients not responding to vasodilator therapy is disappointingly high (39).

Because the lungs of patients with ARDS are extraordinarily stiff, high inflation pressures are required to maintain ventilation. Both the stiff lungs and high inflation pressures are expected to stiffen the cardiac fossa which may contribute to the LV dysfunction present in a high number of these patients.

Pulmonary edema that occurs as the consequence of LV failure, and that which occurs as the result of lung injury (ARDS), are usually distinguishable on the basis of accompanying history and other clinical criteria. When doubt exists or when it would be judicious to have more information regarding left ventricular filling pressure to make clinical decisions, especially in regards to fluid therapy, pulmonary arterial wedge pressures are obtained. If the individual is not receiving positive pressure ventilatory therapy, or if airway pressures remain low, these pulmonary wedge pressures have been interpreted as though the heart were in normal surroundings. If the hemodynamic situation that caused the pulmonary edema were still present at the time wedge pressure measurements were being made, high pulmonary capillary pressures (i.e., > 15 mmHg) would indicate a hydrostatic propensity to develop pulmonary edema. A moderate to low pressure (i.e., < 15 mmHg) would be suggestive of a leaky pulmonary vascular bed. The causes for a high wedge pressure usually are thought to be a failing LV ventricle, a volume overloaded state in a normal ventricle, or restrictive LV disease. Hypothetically, the cardiac fossa and the LV system might be stiff because of the stiffness of the adjacent edematous lung. If the LV system were stiff, these high hydrostatic pressures might occur without the LV being sufficiently filled to maintain cardiac output at desired levels.

3. PEEP

Controlled ventilation with positive airway pressure especially with positive end-expired pressure (referred to as PEEP) has been employed in patients with pulmonary edema caused by lung injury (35,38,39). Two purposes are served by this mode of respiratory therapy. First, controlling ventilation has the potential to reduce the work of breathing and thereby lower the metabolic oxygen demand. Secondly, adding a threshold pressure to expiration, below which airway pressure will not be allowed to fall, prevents the lungs from exhaling to a lower volume at which more alveolae would be unstable and more would collapse. This prevention of atelectasis reverses

some of the hypoxemia that is caused by pulmonary edema. Both of these benefits of this form of respiratory therapy should improve systemic oxygen transport. The recognition that positive pressure ventilation with PEEP has the potential to lower cardiac output and oxygen transport set a limit to the usefulness of this therapy. However, if the mechanisms responsible for the reduction in cardiac output could be identified and corrected, the benefits of ventilation with PEEP with respect to oxygen transport would be greater.

Therefore, for the past 12 years, investigation into potential mechanisms responsible for adverse cardiovascular effects of PEEP have been intense, and the result of these investigations has generated the majority of the data that have advanced our understanding of heart-lung interactions which extends beyond the area of the cardiovascular effects of PEEP. In fact, the term heart-lung interactions was coined by Robotham and colleagues to describe those mechanical phenomena that could not be explained by our prior understanding of ventricular interactions and the lung expansion-induced alterations in pleural pressure (26).

The enlightening studies that showed that positive pressure lung expansion will decrease the compliance of the cardiac fossa and of the left ventricular system have been presented. Therefore, the futile attempts to explain the hemodynamic data that occurred in response to ventilation with PEEP of prior studies without the appreciation of the contribution of the fossa to these phenomena will not be repeated. It will be sufficient to say that in response to ventilation with PEEP, LV and RV end-diastolic volumes were proportionally reduced in spite of elevations in mean atrial or end-diastolic pressures, and the elevations in these pressures were out of proportion to the elevations in pleural pressures (40-42).

Using techniques of biplane cineradiography of dogs whose hearts are implanted with radiopaque markers, we have learned more about the PEEP-induced decrease in the compliance of the fossa and its contents, especially the LV. Ventilation with PEEP does not decrease cardiac output by symmetrically reducing all LV end-diastolic dimensions as would occur during hemorrhage. Rather, PEEP causes a disproportionate reduction in the septal-lateral LV dimension and hardly any reduction in LV anteroposterior dimension (43) (Fig. 18). It had been proposed that the mechanism by which PEEP could reduce LV volume and its septal-lateral dimension might be through a ventricular interdependence mechanism (42). PEEP was thought to increase PVR and PA pressure thereby increasing RV end-diastolic volumes creating a leftward shift of the septum which lowers LV compliance. Because of this alleged potential to shift the septum leftward, we examined the disproportionate reduction in septal to lateral dimension by determining the relative displacements of the septum and the lateral wall from the center of the LV. We were surprised to learn that the septum was shifted to the center of the LV only as much as the anterior and posterior walls were. It was the lateral LV wall that was shifted inward disproportionately by ventilation with PEEP. These relative shape changes were amplified when LV volume was restored by I.V. fluid administration (Fig. 18b). The lateral wall remained shifted inward, and LV end-diastolic volume was restored by outward displacement of the anterior and posterior walls and actually a rightward displacement of the septum. These findings are consistent with an increase in radius of curvature of the septum.

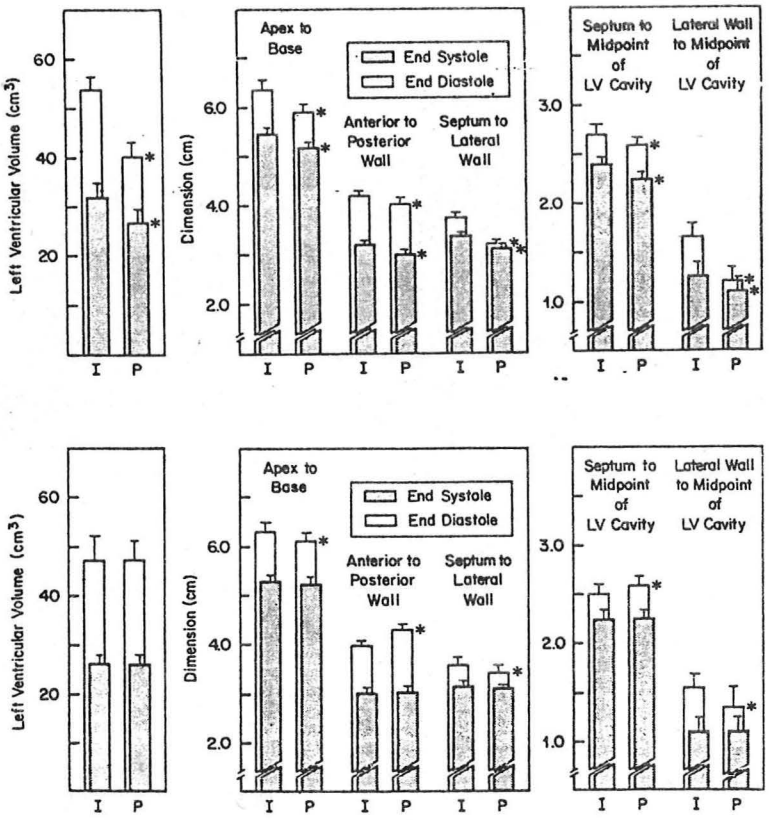

Figure 18 LV volume and dimensions before and in response to 10 cm H_2O PEEP (A), and with and without 10 cm H_2O PEEP after i.v. volume adjustment to equalize LV end-diastolic volume (B).

Formerly, the only interpretation of an increase in radius of curvature of the septum which is found in patients ventilated with PEEP had been a leftward shift of the septum (42), but stretching in the anteroposterior direction also increases the septal radius of curvature. The reasoning to suggest that the septum would be shifted was not supported by clinical or experimental evidence because PEEP rarely increases PA pressures in spite of increasing PVR because of the PEEP-associated reduction in cardiac output.

The increased stiffness of the lateral wall of the fossa is also illustrated in the dynamic graphic presentations of cardiac dimensions (Fig. 19) (43). Normally, during arrested ventilation, the three axial dimensions shorten as expected during ejection and widen as expected during the rapid and slow filling phases. During arrested ventilation with 10 cm H2O PEEP, the long or major axis of the LV and the anteroposterior axis exhibit the normal expected pattern of shortening during ejection and of widening during filling. The septal-lateral dimension, however, did not move normally. Rather than shortening during the ejection period, this dimension actually widened for the first half of ejection. Subsequent narrowing was to an end-systolic width that was only slightly less than at end-diastole. It was as though the ventricle at diastole were flattened by the intrathoracic forces, then resumed its spheroid shape with systolic contraction. The septal to lateral dimension did not move normally during the relaxation phase either.

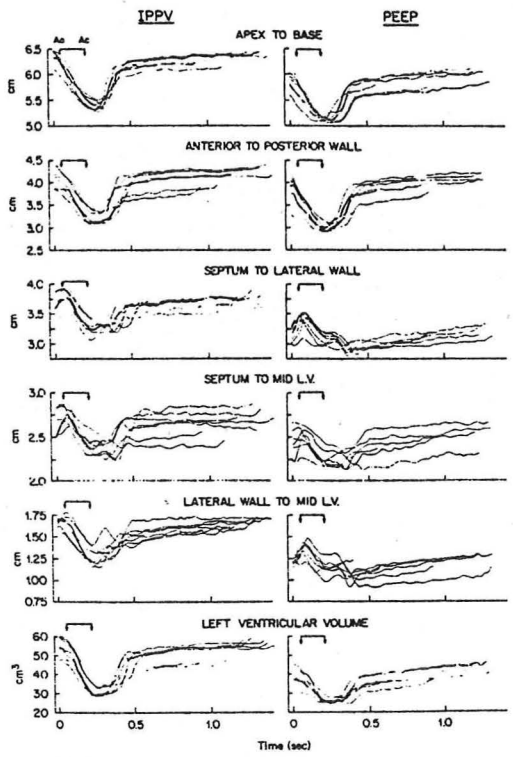

Figure 19 Left ventricular dimensions and volumes plotted throughout 1 cardiac cycle beginning and ending with an R wave in each of 6 dogs. Timing of aortic opening (Ao) and closing (Ac) was recorded in 2 dogs. These data correspond to those in Figure 18a.

At end of systole when the other dimensions were undergoing very rapid expansion, the septal to lateral wall abruptly narrowed again, as though the lung overlying the lateral surface were exerting a lot of pressure on the lateral wall which it actually is reported to do (26a). Examining the relative movements of the septum and lateral wall reveals that this unexpected septal-lateral motion is abnormal lateral wall motion not abnormal septal motion.

Not nearly so much data exists for the effects of PEEP on the RV. Clearly, RV volume is reduced by PEEP (40-43a), but the effect of PEEP on RV shape, compliance, ejection and wall motion are unresolved. PA pressures usually are not elevated substantially by PEEP per se. When PA pressures are not elevated substantially by PEEP, there would be no substantial increase in RV volume to reduce LV compliance and volume. The effects of lung expansion on RV system compliance has not been investigated.

From the studies of Lloyd and Wallis et al. (25,26), we learned that the compliance of the LV septum and the cardiac fossa was reduced when the lungs were distended with positive airway pressure meaning that larger pressures were required to fill the LV or fossa than could be explained by the elevation in pleural or esophageal pressures. From studies on LV dimensions we learned that one reason for the fall in LV compliance was increased eccentricity of the lateral LV wall caused by direct compression of the lateral LV wall by the adjacent distended stiff lung.

The degree to which this LV compression takes place would depend on the associated mechanical factors of lung volume, lung compliance, airway pressure, and RV volume and pressure. The increase in LV pressure caused by the decrease in LV system compliance cannot be estimated from pleural pressure. However, the increase in LV pressure caused by the decrease in LV system compliance probably can be estimated from wedge pressure measurements that are made by abruptly removing the elevated airway pressure (i.e., disconnecting the ventilator from the endotracheal tube for 5-10 seconds). The immediate fall in wedge pressure (1-2 heartbeats) before increased venous return to the RV can reach the LV is felt to be caused by a return of the LV compliance to that which would occur without the added airway pressure. That is, LV end-diastolic volume would remain the same, only the LV compliance would increase, and therefore the wedge pressure would fall. Presuming normal intrinsic LV compliance and accurate methods of obtaining wedge pressures, the relative state of LV filling could be estimated. Thus, if wedge pressures were to fall to 5-6 mmHg, the LV end-diastolic size would not be expected to be very large. Clinical decisions about whether to increase LV filling would be judged (among other clinical data) on the wedge pressure measurements made during ventilation which determines capillary filtration while being ventilated and the wedge pressure measurements made immediately off the ventilator which estimates LV end-diastolic size. The extent of the abrupt fall in wedge pressure is a measure of reduction in LV compliance that is caused by PEEP-induced heart-lung interaction. The wedge pressure measured off PEEP will increase fairly rapidly as the venous return increases so the measurements made off PEEP have to be made immediately, this usually would require a strip recording of the maneuver rather than an inspection of the monitor screen.

We have considered primarily the adverse effects of positive pressure ventilation on LV diastole. But positive pressure ventilation has the potential to assist systole in the same way that it tends to empty the ventricle in diastole. In the failing heart, the LV can be unloaded by augmenting the pressure surrounding the heart just the same as by lowering intra-arterial pressure. In order to maximize unloading and minimize adverse effects on filling, positive pressure ventilation has been coupled to cardiac contraction by synchronizing the ventilatory cycle to the EKG. Pinsky and associates (44,45) have shown that synchronizing systole with the inspiratory cycle of a ventilator, which is set to deliver very large tidal volumes thereby achieving maximal lung expansion and pressures, improves LV ejection in the presence of LV failure.

4. Impact of heart-lung interactions on cardiac diseases.

Apart from ventricular interdependence, heart-lung interactions are beginning to have an impact on heart disease in two areas: Cardiopulmonary resuscitation (CPR) and as a stress for detecting myocardial ischemia.

Interest in understanding the mechanisms by which CPR can sustain circulation was renewed by Criley and associates (46) who reported that circulation could be maintained by coughing during cardiac arrest. Subjects undergoing cardiac catheterization were trained to be prepared to cough upon instruction. When ventricular fibrillation occurred, the patients coughed

every 1-2 seconds until defibrillation could be performed. Patients were kept conscious during arrest for as long as 1.5 min by coughing. This raised questions as to what are the actual mechanical events that create circulation during cardiac arrest and CPR that are under investigation.

Another interesting outgrowth of the heightened understanding of heart-lung interactions is that reported very recently by Scharf et al. (47) of using a Müller maneuver as a stress to precipitate myocardial ischemia. He has demonstrated that the extreme negative pressures of a Müller maneuver cause S-T segment depression in patients who also were shown to have S-T depression on exercise testing. If these findings are validated, they have important implications regarding the stress to the myocardium caused by heavy ventilatory work loads in addition to the potential usefulness of a Müller in detecting occult ischemia.

In summary, the interactions between the lungs and heart have been described at three levels. First were their interactions at the level of gas exchange where the heart and lungs are linked together to ventilate, diffuse, carry, deliver, and distribute oxygen to meet the aerobic requirements of the various tissues of the body. The capacities of this delivery system are such that its limits are not reached except at heavy exercise or in advanced respiratory or cardiac disease. The needs for O2 uptake and CO2 delivery drive both systems, and the O2 and CO2 contents of the blood have direct and reflex actions on both respiratory and cardiovascular systems that are independent of O2 and CO2 delivery needs.

The remainder of the heart-lung interactions reflects a unidirectional bias of lung mechanisms acting on the heart. Apart from the respiratory gases, reflex and humoral mechanisms exist whereby the lung exhibits regulatory control over cardiovascular function. These reflexes are evoked by both mechanical (lung inflation) and nonrespiratory chemical stimulation of the lungs. The homeostatic functions that are served by these reflexes are largely unknown.

The mechanical interactions receive the most interest, and the preponderance of recent data is concerned with the effects of altered respiratory system mechanics on the heart. These effects are mediated through elevated PA pressures that lower LV system compliance by virtue of enlarged RV volumes and through changes in stiffness and/or volume of the lungs and thorax that likewise lower LV system compliance.

Thus, heart-lung interactions are a complex mixture of responses to altered mechanical and chemical milieu. These environments must be separated in order to learn their individual potential. In the practice of clinical medicine, our understanding of pathophysiological processes that involve the heart and lungs often requires us to consider the potential of each of these interactions, and to base clinical judgement on an integration of these complex interactions.

The following statement was made nearly 100 years ago, but it is pertinent regarding the recent appreciation of heart-lung interactions.

> "The experimental results which we wish to bring forward are largely such as might be predicted by anyone with a knowledge of the elementary principles of the circulation. Our justification in bringing them forward is that they have not been so predicted, and it was only after obtaining the results that we asked ourselves why they had not occurred to us before."
>
> BAYLISS AND STARLING, 1894.

This statement was made in response to generating the data on which Starling's law of the heart was founded. The same statement could have been made upon the realization of the existence of ventricular interdependence, and more recently upon the realization of mechanical heart-lung interactions that are mediated through the cardiac fossa.

REFERENCES

1. Johnson RL Jr.: Exercise testing in lung disease, Chapter 12, in Sackner M (ed): Diagnostic Techniques in Pulmonary Disease, Pt. I. New York, Marcel Dekker, 1980. (Available from Pulmonary Research Office, H8.112)

2. Johnson RL Jr.: Oxygen transport, in Willerson JT and Saunders CA (ed): Clinical Cardiology. The Science and Practice of Clinical Medicine. New York, Grune and Stratton, 1977.

3. Beierholm EA, Grantham RN, O'Keefe DD, Laver MB, Daggett WM: Effects of acid-base changes, hypoxia, and catecholamines on ventricular performance. Am J Physiol 228:1555-1561, 1975.

4. Sonnenblick EH, Kirk ES: Effects of hypoxia and ischemia on myocardial contraction. Cardiology 56:302-313, 1972.

5. Eyzaguirre C, Fitzgerald RS, Lahiri S, Zapata P: Arterial chemoreceptors, in Shepherd JT and Abboud FM (ed): Handbook of Physiology, Section 2: The Cardiovascular System, Volume III: Peripheral Circulation and Organ Blood Flow, Part 2. Baltimore, Williams and Wilkins, 1983, p 557-621.

6. Coleridge JCG and Coleridge HM: Chemoreflex regulation of the heart, Chapter 18, in Berne RM (ed): Handbook of Physiology, Section 2: The Cardiovascular System, Volume I: The Heart. Baltimore, Williams and Wilkins, 1979, p 653-676.

7. Fitzgerald RS and Lahiri S: Reflex responses to chemoreceptor stimulation, Chapter 10, in Fishman AP (ed): Handbook of Physiology, Section 3: The Respiratory System, Volume II: Control of Breathing, Part 1. Baltimore, Williams and Wilkins, 1986, p 313-362.

8. Grover RF, Wagner WW Jr, McMurtry IF, Reeves JT: Pulmonary circulation, Chapter 4, in Berne RM (ed): Handbook of Physiology, Section 2: The Cardiovascular System, Volume III: Peripheral Circulation and Organ Blood Flow. Baltimore, Williams and Wilkins, 1983, p 103-136.

9. Harris P and Heath D: Pulmonary hemodynamics in chronic bronchitis and emphysema, Chapter 34, in The Human Pulmonary Circulation. New York, Churchill Livingstone, 1977, p 522-546.

10. Coon RL, Zuperku EJ, Kampine JP: Respiratory arrhythmias and airway CO2, lung receptors, and central inspiratory activity. J Appl Physiol 60:1713-1721, 1986.

11. Cassidy SS, Eschenbacher WL, Johnson RL Jr: Reflex cardiovascular depression during unilateral lung hyperinflation in the dog. J Clin Invest 64:620-626, 1979.

12. Ashton JH and Cassidy SS: Reflex depression in ventricular contractility and vascular tone during unilateral lung inflation in anesthetized dogs. J Appl Physiol 58:137-145, 1985.

13. Kaufman MP, Iwamoto GA, Ashton JH, Cassidy SS: Responses to inflation of vagal afferents with endings in the lung of dogs. Circ Res 51:525-531, 1982.

14. Cassidy SS: Stimulus-response curves of the lung inflation cardiodepressor reflex. Respir Physiol 57:259-268, 1984.

15. Cassidy SS, Ashton JH, Wead WB, Kaufman MP, Monsereenusorn Y, Whiteside JA: Reflex cardiovascular responses caused by stimulation of pulmonary C fibers with capsaicin in dogs. J Appl Physiol 60:949-958, 1986.

16. Wead WB, Cassidy SS, Coast JR, Hagler HK, Reynolds RC: Reflex cardiorespiratory responses to pulmonary vascular congestion. J Appl Physiol 62:No. 2, 1987.

17. Wead WB, Cassidy SS, Reynolds RC: Cardiopulmonary reflex responses to pulmonary edema in the dog. Am J Physiol, 252:No. 2, 1987.

18. Dunham BM, Grindlinger GA, Utsunomiya T, Krausz MM, Hechtman HB, Shepro D: Role of prostaglandins in positive end-expiratory pressure-induced negative inotropism. Am J Physiol 241:H783-H788, 1981.

19. Patten MT, Liebman PR, Hechtman HB: Humorally mediated decreases in cardiac output associated with positive end-expired pressure. Microvasc Res 13:137-139, 1977.

20. Pitt BR, Lister G, Gillis CN: Hemodynamic factors affecting lung metabolism, in Ryan US (ed): Pulmonary Endothelium in Health and Disease. New York, Marcel Dekker, 1987.

21. Gillis CN and Catravas JD: Altered removal of vasoactive substances in the injured lung: detection of lung microvascular injury. Ann NY Acad Sci 384:458-474, 1982.

22. Braunwald E and Ross J Jr: Control of cardiac performance, Chapter 15, in Berne RM (ed): Handbook of Physiology, Section 2: The Cardiovascular System, Volume I: The Heart. Baltimore, Williams and Wilkins, 1979, p 533-579.

23. Ross J Jr, Covell JW, Sonnenblick EH, Braunwald E: Contractile state of the heart characterized by force-velocity relations in variably afterloaded and isovolumic beats. Circ Res 18:149-163, 1966.

24. Janicki JS and Weber KT: The pericardium and ventricular interaction, distensibility, and function. Am J Physiol 238:H494-H503, 1986.

24a. Agostoni E and Mead J: Statics of the respiratory system, Chapter 13. In Fenn WO and Rohn H (ed): Handbook of Physiology, Section 3: Respiration, Volume I, Washington, DC, Am Physiol Soc, 1964, 387-409.

25. Lloyd TC Jr: Respiratory system compliance as seen from the cardiac fossa. J Appl Physiol 53:57-62, 1982.

26. Wallis TW, Robotham JL, Compean R, Kindred MK: Mechanical heart-lung interaction with positive end-expiratory pressure. J Appl Physiol 54:1039-1047, 1983.

26a. Fewell JE, Abendschein DR, Carlson CJ, Rapaport E, Murray JF: Mechanisms of decreased right and left ventricular end-diastolic volumes during continuous positive pressure ventilation in dogs. Circ Res 47:467-472, 1980.

26b. Marini JJ, O'Quin R, Culver BH, Butler J: Estimation of transmural cardiac pressures during ventilation with PEEP. J Appl Physiol 53:384-391, 1982.

26c. Robertson CH Jr, Hall DL, Hogg JC: A description of lung distortion due to localized pleural stress. J Appl Physiol 34:344-350, 1973.

27. Marini JJ, Culver BH, Butler J: Effect of positive end-expiratory pressure on canine ventricular function curves. J Appl Physiol 51:1367-1374, 1981.

28. Hoffman JE, Guz A, Charlier AA, Wilcken DE: Stroke volume in conscious dogs; effect of respiration, posture, and vascular occlusion. J Appl Physiol 20:865-877, 1965.

29. Karam M, Wise RA, Natarajan TK, Permutt S, Wagner HN: Mechanism of decreased left ventricular stroke volume during inspiration in man. Circulation 69:866-873, 1984.

30. Andersen K and Vik-Mo H: Effects of spontaneous respiration on left ventricular function assessed by echocardiography. Circulation 69:874-879, 1984.

31. Wead WB and Norton JF: Effects of intrapleural pressure changes on canine left ventricular function. J Appl Physiol 50:1027-1035, 1981.

32. Cassidy SS, Wead WB, Seibert GB, Ramanathan M: Changes in left ventricular geometry during spontaneous breathing. J Appl Physiol In Press, 1987.

33. Robotham JL, Lixfeld W, Holland L, MacGregor D, Bryan AC, Rabson J: Effects of respiration on cardiac performance. J Appl Physiol 44:703-709, 1978.

34. McFadden ER Jr and Braunwald E: Cor pulmonale and pulmonary thromboembolism, Chapter 46. In Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, Volume 2. Philadelphia, Saunders, Ed. 2, 1984, p 1572-1604.

35. Matthay RA, Matthay MA, Dantzker DR (eds): Cardiovascular-pulmonary interaction in normal and diseased lungs. Clinics in Chest Medicine, Volume 4/Number 2. Philadelphia, Saunders, May 1983.

36. Khaja F and Parker JO: Right and left ventricular performance in chronic obstructive lung disease. Am Heart J 82:319-327, 1971.

37. Matthay RA, Berger HJ, Davies RA, Loke J, Mahler DA, Gottschalk A, Zaret BL: Right and left ventricular exercise performance in chronic obstructive pulmonary disease: Radionuclide Assessment. Ann Int Med 93:234-239, 1980.

38. Zimmerman GA, Morris AH, Cengiz M: Cardiovascular alterations in the adult respiratory distress syndrome. Am J Med 73:25-34, 1982.

39. Zapol WM and Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476-480, 1977.

40. Cassidy SS and Mitchell JH: The effects of positive pressure breathing on right and left ventricular preload and afterload. Federation Proceedings 40:2178-2181, 1981.

41. Fewell JE, Abendschein DR, Carlson CJ, Murray JF, Rapaport E: Continuous positive pressure ventilation decreases right and left ventricular end-diastolic volumes in the dog. Circ Res 46:125-132, 1980.

42. Jardin F, Farcot JC, Boisante L, Curien N, Margairay A, Bourdarias JP: Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 304:387-392, 1981.

43. Cassidy SS, Mitchell JH, Johnson RL Jr: Dimensional analysis of the right and left ventricles during positive pressure ventilation in dogs. Am J Physiol 242:H549-H556, 1982.

43a. Cassidy SS and Ramanathan M: Dimensional analysis of the left ventricle during PEEP: relative septal and lateral wall displacements. Am J Physiol 246:H792-H805, 1984.

44. Pinsky MR, Summer WR, Wise RA, Permutt S, Bromberger-Barnea B: Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol 54:950-955, 1983.

45. Pinsky MR and Summer WR: Cardiac augmentation by phasic high intrathoracic pressure support in man. Chest 84:370-375, 1983.

46. Criley JM, Bloufuss AH, Kissell GL: Cough induced cardiac compression. J Am Med Assoc 263:1246-1250, 1976.

47. Scharf SM. Muller maneuver causes ischemic electrocardiographic changes in patients with coronary disease. Ann Biomed Engineering 15:No. 3, 1987.