THERAPEUTIC UNLOADING OF PATIENTS WITH CHRONIC HEART FAILURE

MEDICAL GRAND ROUNDS

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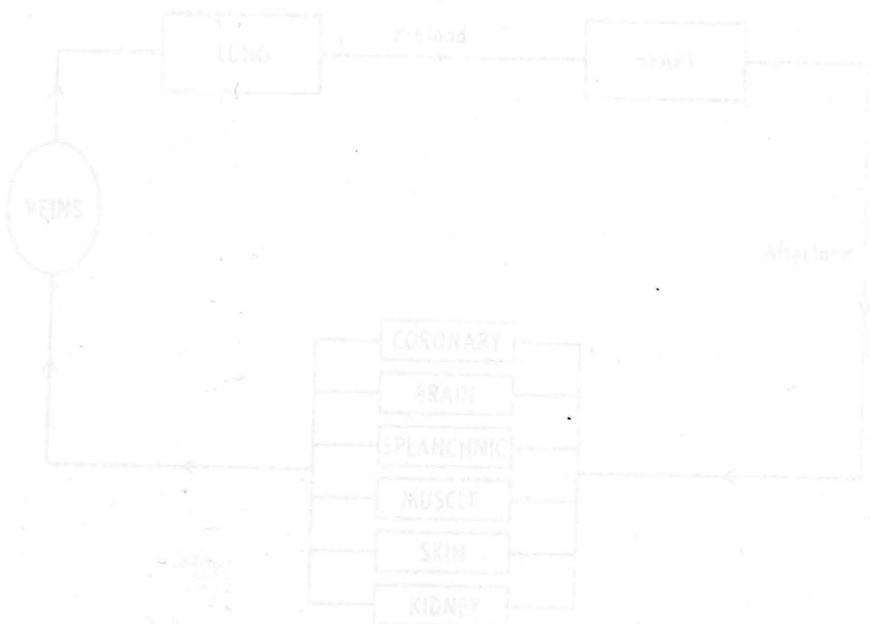


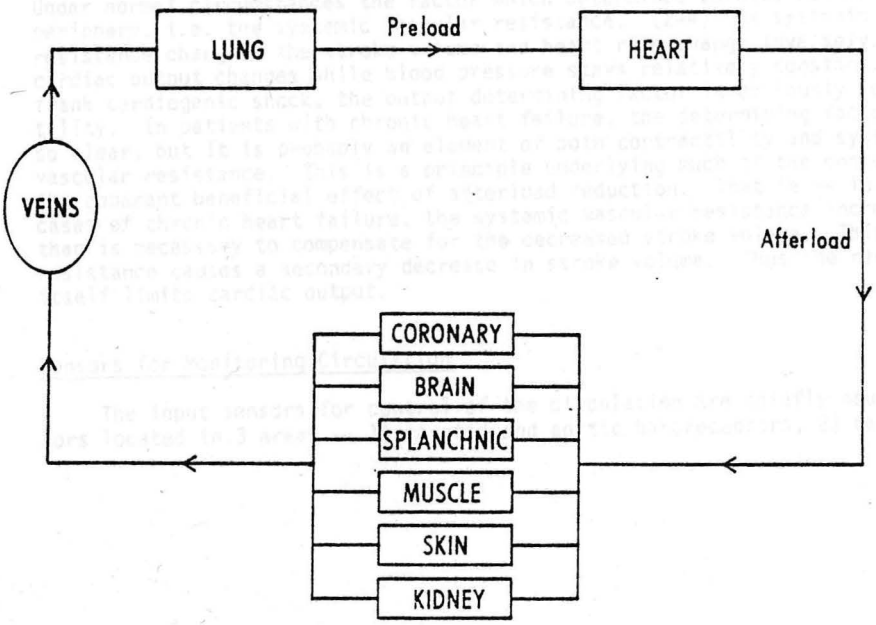
Introduction

"Unloading" as therapy for heart failure is a currently popular subject in cardiology. While many of the physiologic principles underlying the concept of unloading have been known for some time, the aggressive investigation and therapeutic use of these concepts has acquired momentum in only the last 6-7 years. The subject is confusing partly because it is a field under intense investigation in which new information is accumulating rapidly. Since Dr. Mitchell last reviewed the subject in these Grand Rounds 3 years ago, (1) considerable progress has been made. However, unloading is also confusing because the field encompasses much physiology in multiple organ systems which are linked by the circulation and respond to changes in an integrated fashion.

In the discussion today, I will first summarize what is known and not known about the control of the circulation in the normal and heart failure state. Then I will summarize how the circulation attempts to compensate for the failing heart, emphasizing those aspects pertinent to the concept of unloading. Then finally, I will review current concepts regarding how these compensatory changes can be therapeutically modified to benefit the patient.

Preview Summary of Pathophysiology

To carry out its purpose of transporting oxygen and other metabolites throughout the body, the circulatory system must be closely controlled. The system must be controlled such that venous and aortic pressure, cardiac output and its distribution, systemic vascular resistance, and the heart function as an integrated unit. A particular problem when dealing with the whole body circulation is that it is sometimes difficult to discern cause and effect because of the complex feedback nature of the control, i.e. a chicken and egg effect. For instance, it is frequently difficult to determine what element in the overall circulation determines the cardiac output.



The above diagram will be used repetitively throughout this discussion. Much of the pathophysiology to be discussed can be envisioned by imagining blood flowing through the circuit.

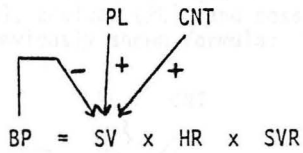
Of all the variables in the circulatory system, the aortic blood pressure seems to be the most zealously guarded by the body's control mechanisms. The relationship between aortic pressure (BP), cardiac output (CO), and systemic vascular resistance (SVR) is given by the equation:

$$BP = CO \times SVR$$

Since CO is the product of heart rate (HR) and stroke volume (SV), the equation can be expanded to:

$$BP = SV \times HR \times SVR$$

This interrelationship can be further expanded by indicating the positive influence of preload (PL) and myocardial contractility (CNT) on stroke volume, and the negative influence of BP.



In these diagrams x and = signs indicate a mathematical relationship while arrows indicate a controlling influence. This relationship is obviously interdependent and circular. The question arises -- what limits cardiac output. Under normal circumstances the factor which determines cardiac output is the periphery, i.e. the systemic vascular resistance. (2-4) As systemic vascular resistance changes, the stroke volume and heart rate change inversely. Thus cardiac output changes while blood pressure stays relatively constant. In frank cardiogenic shock, the output determining factor is obviously contractility. In patients with chronic heart failure, the determining factor is not so clear, but it is probably an element of both contractility and systemic vascular resistance. This is a principle underlying much of the concept of the apparent beneficial effect of afterload reduction. That is -- in many cases of chronic heart failure, the systemic vascular resistance increases more than is necessary to compensate for the decreased stroke volume. This increased resistance causes a secondary decrease in stroke volume. Thus the resistance itself limits cardiac output.

Sensors for Monitoring Circulation

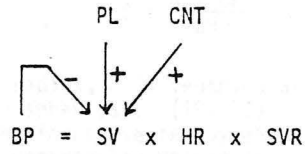
The input sensors for control of the circulation are chiefly neural receptors located in 3 areas -- 1) carotid and aortic baroreceptors, 2) cardiopulmonary

mechanoreceptors located in the atrial and ventricular wall, 3) somatic receptors located in skeletal muscle. The carotid and aortic baroreceptors respond to mean aortic pressure and the rate of change of pressure. (5-7) The cardiopulmonary mechanoreceptors respond to transmural pressure in the atria and ventricles, and to atrial and ventricular contraction. (6, 8, 9) The somatic receptors respond to movement of skeletal muscle and muscle hypoxia. (10, 11) Chemoreceptors also play a role when blood gases are altered, but these receptors will not be considered further. (12) The peripheral vasculature is also under local control in each organ bed. (6)

The input from the baroreceptors, cardiopulmonary mechanoreceptors, and somatic receptors are fed to the brain where they are integrated in a frequently complex manner. (11) The output from the vasomotor center is via hormonal and/or neural mechanisms.

Acute Circulatory Response to Sensor Input

The acute response to input from the circulatory control network in the healthy circulation is the response expected to maintain aortic blood pressure (BP). The response is mediated via changes in the heart rate (HR), systemic vascular resistance (SVR), preload (PL), and possibly contractile state (CNT); as illustrated by the previously shown formula:



Acutely, alterations in aortic pressure affect the carotid and aortic baroreceptors which generate a compensatory response by changing heart rate, systemic vascular resistance, and possibly contractility. Preload may also respond through changes in venous tone. (6, 11) Alterations in pressure or stretch of the cardiopulmonary mechanoreceptors are harder to study because the receptor network is more diffuse and secondary effects are harder to control. However, the chief response seems to be an increase in systemic vascular resistance and a retention of sodium. (6, 9, 13) In the intact healthy person, the receptors feed their information to the vasomotor center where the responses from all of the receptors are integrated in a complex manner to obtain a unified response. (11)

Preload

Preload is maintained at the proper level by the relationship between blood volume and venous tone. Blood volume is regulated by the rate of sodium excretion relative to sodium intake. The sensory input for this regulatory system is not fully understood, but most evidence points to the cardiopulmonary mechanoreceptors. (6, 9) The vasomotor center signals the kidney as to the proper amount of sodium excretion via the sympathetic nervous system and probably also by a poorly under-

stood hormonal system. (6, 9, 14-16) Renal regulation of sodium excretion is mediated via the amount of tubular reabsorption of sodium, however the actual mechanism is unknown. (14-17)

The importance of venous tone in the maintenance of preload is due to the high compliance of the venous system and the fact that 85% of the blood volume is in the venous system. (6) The 3 most important venous beds are the muscular, cutaneous, and splanchnic. The muscular bed responds chiefly to the pumping action of exercise and the cutaneous bed is chiefly used for thermal regulation. (6) The splanchnic bed is the chief venous bed used by the body for variation of preload. This bed is heavily innervated by sympathetic fibers and receives sensory information via the vasomotor center from the baroreceptors and the cardiopulmonary mechanoreceptors. (6, 11, 18)

Systemic Vascular Resistance

Definition of Afterload. The definition of afterload must be clarified as it is defined differently by different authors. The first clarification is whether one is dealing in terms of blood pressure or wall stress. Wall stress is the contractile force exerted by a square cm of ventricular muscle running parallel to the ventricular surface. The relationship of blood pressure (BP) to wall stress (S) is given by the formula:

$$S = \frac{R \times BP}{2H}$$

Where R is ventricular radius, H is ventricular wall thickness, and the ventricle is assumed to be spherical. (19, 20) Wall stress is the closest practical measurement to the force exerted by each fiber in the ventricular wall. Stress is dependent on ventricular volume as well as wall thickness. During an acute intervention, volume and wall thickness are usually assumed not to change significantly. This assumption is approximately correct. If this assumption is accepted, then wall stress is proportional to aortic blood pressure. Therefore, blood pressure will be used as the measurement of force against which the ventricular fibers contract.

However, another clarification in the definition of afterload is whether the blood pressure (BP) or systemic vascular resistance (SVR) should be used. (21, 22) These 2 terms are related via the cardiac output (CO) by the familiar equation:

$$BP = CO \times SVR$$

In favor of using SVR as the definition of afterload is the fact that SVR does not change with cardiac output. However, the majority of studies of ventricular function measure how the ventricle performs against a pressure load. Consequently, if SVR is used as the measure of afterload, its relationship to ventricular function must be mediated by the effect of SVR on the BP. Consequently,

I have chosen to use BP as the measurement of afterload. However, the chosen definition is less important than an understanding of the relationship.

Finally, a related clarification is the relationship between systemic vascular resistance and aortic input impedance. (21, 22) Both terms refer to the opposition to flow that blood encounters as it flows into the aorta. The major component of impedance is resistance, however impedance takes into account some factors in addition to resistance. (21-25) An overview of impedance is in order since the term is frequently used and is intimidating.

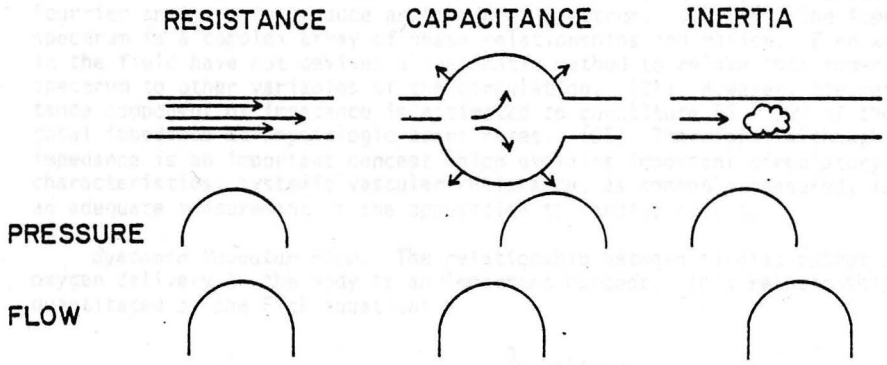
If the systemic circulation were to be composed entirely of resistance in the strict sense, the usual formula for systemic vascular resistance (SVR) of

$$SVR = \frac{BP}{CO}$$

where BP = Blood Pressure

CO = Cardiac Output

would hold at every instant in time. Another way of stating this is that pressure and flow are in phase, and therefore they instantaneously vary in direct proportion to each other. This relationship is shown in the diagram below.



In this pure resistance system, there would be no elasticity or capacitance of vessels, i.e. the vascular system would be composed of rigid pipes. Therefore flow would only occur when there was pressure or during systole. If systole occurs during 1/3 of the cardiac cycle, the pressure and flow would have to be 3 x as high during systole as it would have to be to maintain the same mean flow under the normal situation where flow occurs continuously.

Fortunately, however, the arterial system is elastic and therefore the large and medium sized arteries can store blood in them. This storing ability is called capacitance. A characteristic of capacitance is that flow into the capacitance chamber is not directly proportional to the pressure at the mouth of the chamber. Flow into a pure capacitance chamber is initially brisk with low pressure. As the chamber fills however, flow decreases as pressure builds up. Finally, when the chamber is full, pressure is maximum and flow is zero. Therefore, unlike resistance, pressure and flow are out of phase in a capacitance system. Consequently, the simple ratio of pressure/flow can no longer be directly applied since it will vary depending on the point in the flow cycle at which it is measured. Similarly, blood has mass and therefore inertia. This introduces another variation in the phase relationship because some pressure must be expended in "getting the blood moving". Consequently, because of inertia, the pressure during parts of the cycle may "lead" the flow, whereas with capacitance, the flow "leads" the pressure.

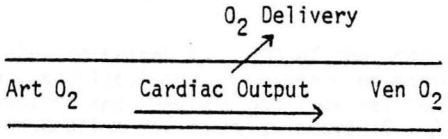
Therefore, impedance is composed of the three basic elements of resistance, capacitance, and inertia. Of these 3 elements, only resistance uses up energy. Capacitance and inertia merely store the energy of the heart and release it at a different time into the arterial system. Since capacitance and inertia do not dissipate energy, their chief importance to the hemodynamic situation is the "matching" of the heart to the peripheral vasculature. Proper matching allows the conversion of myocardial energy to systemic flow as efficiently as possible. Fortunately, it appears that the combination of factors are appropriate in the human cardiovascular system for efficient operation.

Measurement of impedance is complex necessitating a system called Fourrier analysis to produce an impedance spectrum. (23, 25) The impedance spectrum is a complex array of phase relationships and ratios. Even workers in the field have not devised a systematic method to relate this impedance spectrum to other variables of the circulation. (21) However, the resistance component of impedance is estimated to constitute 95 - 98% of the total impedance at physiologic heart rates. (25) Therefore, although impedance is an important concept which explains important circulatory characteristics, systemic vascular resistance, as commonly measured, is an adequate measurement of the opposition to cardiac output.

Systemic Vascular Flow. The relationship between cardiac output and oxygen delivery to the body is an important concept. This relationship is quantitated by the Fick equation:

$$\text{Cardiac Output} = \frac{O_2 \text{ Delivery}}{\text{Art - Ven } O_2 \Delta}$$

shown diagrammatically as:



Oxygen delivery is therefore dependent on the difference in oxygen concentration of the arterial and venous blood (i.e. how much oxygen is extracted from each ml of blood) as well as the cardiac output. This point bears emphasis. For a given oxygen delivery to the body, cardiac output can vary widely.

When the peripheral vasculature is considered in terms of each organ, the relationship between the percentage of cardiac output, the percentage of oxygen extracted from each ml of blood, and the percentage of body oxygen consumed varies considerably from organ to organ. (26) These relationships are pictured in the table below. (6)

	Relative Flow (% Cardiac Output)	Relative A - VO_2 Δ (% O_2 Extracted)	Relative O_2 Consumption (% Body O_2 Consumption)
Heart	4	58	12
Brain	13	32	20
Splanchnic	26	21	25
Muscle	19	32	29
Skin	9	5	2
Kidney	21	7	7

Notice that heart and muscle, organs with high oxygen consumption, have a high relative A - VO_2 Δ. Contrast this to organs such as the skin and kidney where blood flow serves more important functions than oxygen delivery. In these organs, blood flow is high relative to oxygen consumption, resulting in a low relative A - VO_2 Δ.

The blood flow to each organ is normally constant, despite changes in blood pressure, secondary to a process called auto regulation. This auto regulation is normally present to some degree in all organs, but is especially active in the brain, heart, and kidney. (6, 18, 26) Auto regulation is active between blood pressures of approximately 80 mmHg and 250 mmHg. Below and above this range of values, organ blood flow is dependent on arterial pressure. The rationale for the common clinical dictum of keeping arterial pressure at 80 mmHg

or above is based on the fact that below 80 mmHg, organ flow decreases.

Exercise

Skeletal muscle comprises 40 - 50% of the body mass of the average man. During severe exercise, local muscle oxygen consumption may increase 100 x the resting consumption and muscle blood flow may increase 25 x. (27) Overall body oxygen consumption may increase about 15 - 20 x. Body oxygen delivery is the product of heart rate x stroke volume x A - VO_2 Δ. In the normal man, the 15 - 20 x increase in oxygen delivery is met by a heart rate approximately 3 x rest value, stroke volume 1 - 1 ½ x rest value, and an A - VO_2 Δ 3 - 4 x rest value. (27, 28) Cardiac output therefore increases to about 4 x rest value.

The fundamental event causing the increase in cardiac output is metabolic vasodilatation of the exercising skeletal musculature. (11, 18, 27) The mechanism by which heart rate increases is not clearly known, but it is probably due to a reflex from the contracting muscle. (11, 27) This reflex also probably causes a contraction in the splanchnic venous bed. This contraction, in conjunction with the pumping action of the skeletal muscles, causes an increase in preload which increases the stroke volume. (11) Thus, during the normal course of exercise, the peripheral vasculature, not the heart per se, is responsible for the increase in cardiac output. (27)

During exercise, myocardial blood flow increases relative to the increase in myocardial oxygen demand. Cerebral blood flow remains constant. Skin blood flow initially decreases, and later increases consistent with the need to eliminate heat. (6, 11, 27) The changes in myocardial, cerebral, and skin blood flow are small, however, relative to the overall changes in cardiac output with exercise. More important are the changes in the relatively high flow splanchnic and renal circulation. Studies in man indicate that flow in the splanchnic and renal circulation decreases in direct proportion to the amount of exercise, until flow is 20% of normal at maximum exercise. (18, 27) There is some skepticism of these results since the methodology in these human studies was indirect and another study using directly instrumented dogs undergoing maximum exercise showed no change in flow. (29) However, the probable explanation is species difference, and the human studies showing decreased flow are generally accepted. (11, 27) The reflex causing this decreased flow probably originates in the exercising muscle. (11, 18)

The systolic blood pressure at maximum exercise ranges from 190 - 240 mmHg. (30) Considering the marked changes in cardiac output, organ blood flow, and individual organ resistances, the precision of the regulation of the cardiovascular system can be appreciated. If the interaction of these marked hemodynamic changes were not closely coordinated, the arterial blood pressure would not stay within its narrow physiologic confines. This could obviously result in catastrophic cerebral or coronary events.

Sensor Mechanism in Heart Failure

When the heart fails, the stroke volume (SV) for a given level of preload decreases. As in the nonfailing circulation, the most zealously guarded major variable in the circulation appears to be the aortic blood pressure. The circulation attempts to restore blood pressure by increasing stroke volume via increased preload and/or by increasing systemic vascular resistance. The question arises as to how the circulatory system senses the presence of heart failure such that these compensatory mechanisms can be activated and circulatory control maintained. This control of the system in the presence of failure is not understood. The sensor mechanisms which are operative in the healthy circulation appear to either be inoperative or function paradoxically in the presence of failure.

Since the aortic blood pressure seems to be so well guarded, the carotid and aortic baroreceptors are possible mediators of the increase in systemic vascular resistance. In the nonfailing circulation, the baroreceptor response to arterial blood pressure change is a change in heart rate and systemic vascular resistance. However, in the animal model of heart failure (31, 32) and in patients with heart failure, (33) the heart rate response to a change in blood pressure is markedly attenuated. This attenuation of the heart rate response can be duplicated by heavy intravascular volume loading, implying that severe stimulation of the cardiopulmonary mechanoreceptors depresses the baroreceptor response. (32) The overall conclusion from these studies is that the function of the baroreceptor is markedly depressed in the presence of heart failure. Another possible conclusion is that the heart rate response of the baroreceptor reflex is depressed, but that the systemic vascular resistance response may be intact. However, another argument against a significant role of the baroreceptor reflex is the fact that blood pressure is usually near normal. For the blood pressure to remain normal while an influence to change blood pressure is operative, the gain of the feedback loop would have to be considerably higher than is found in well controlled studies. (7)

Somewhat related to the arterial baroreceptors is the concept of Effective Arterial Blood Volume (EABV). (14-16, 34) This concept attempts to explain the fact that the body retains sodium and increases systemic vascular resistance in the divergent situations of hypovolemia, hypervolemic low output heart failure, and high output failure. EABV in some way reflects the filling of the arterial tree and therefore the relationship between cardiac output and peripheral runoff. However, it is as yet an unmeasurable quantity and has not been related specifically to blood pressure or arterial volume. The receptors that sense it have not been located, although the baroreceptors, arterial wall, and kidneys are all suspect. At present EABV is a useful but unproven concept.

The cardiopulmonary mechanoreceptors normally respond to distension of the atria by a decrease in systemic vascular resistance and an increased excretion of sodium. (11, 18, 35, 36) However, in the presence of heart failure and its usually large chamber volumes, sodium is paradoxically retained and systemic vascular resistance increased. (11, 15, 16, 34, 36) The cause of this paradox is unclear. In the dog model of heart failure, distension of the atrium gives

less neural impulses than normally, suggesting that chronic stretch somehow inhibits receptor sensitivity. (37) A clinical observation consistent with this hypothesis is that whereas normal persons decrease their forearm blood flow with standing, presumably due to the decreased stretch of their atrial receptors, patients with heart failure increase their forearm blood flow with standing. (38) An attractive possibility for the paradoxically decreased sensory input from patients with large chambers in heart failure is that the input from the sensors in the ventricular wall is decreased. (36) These sensors respond to the vigor of ventricular contraction which is depressed with heart failure. Somewhat consistent with this hypothesis is the observation that experimental coronary artery embolization, with its attendant increased stimulation of ventricular receptors due to the ischemic paradoxical wall motion, results in an inappropriately low systemic vascular resistance for a given level of hypotension. (8, 39)

The somatic receptors in skeletal muscle respond to a decreased pO_2 by causing systemic vasoconstriction. (10) This reflex would seem most likely to occur during exercise, but possibly occurs during extreme cardiac deterioration. A postulated mechanism leading to systemic vasoconstriction is that muscle blood flow is decreased due to arteriolar sodium retention. This decreases muscle blood flow leading to muscle hypoxia which initiates the reflex. (10)

It is likely that rather than any one of the above sensors being responsible for modulating the response to heart failure that the sensors work together in complex fashion. (8, 11, 40) For instance, in one study the effect of the cardiopulmonary mechanoreceptors was enhanced by denervation of the baroreceptors, (7) while in another study the effect of the baroreceptors was depressed by intravascular volume distension presumably causing extreme stimulation of the mechanoreceptors. (32)

Systemic Vascular Resistance Response to Heart Failure

Cardiac output (CO) and systemic vascular resistance (SVR) are closely linked to one another to keep the arterial pressure (BP) in the normal range. (7)

$$BP = CO \times SVR$$

In discussing this relationship attention is usually focused on either cardiac output or systemic vascular resistance and the other is assumed to be secondary. However, it is not always clear which is primary and which is secondary. Under most physiologic conditions such as exercise, the vascular resistance varies primarily and cardiac output secondarily. (18, 27) The increased cardiac output under these circumstances is generally a result of increased heart rate, increased preload, and probably also an increased contractility. (2, 11, 27, 28, 41, 42) However, under conditions of severe cardiac disease when the cardiac output is decreased, the decreased cardiac output is generally assumed to be primary and the vascular resistance is assumed to be secondarily increased to keep the arterial pressure in the normal range. If it is assumed that the decreased cardiac

output of advanced heart disease is solely due to an inability of the heart to pump any more blood, then therapeutically decreasing vascular resistance would be a frightening experience since the blood pressure could fall drastically. However, the concept of therapeutically decreasing systemic vascular resistance assumes that the increase in systemic vascular resistance is greater than that necessary to compensate for the decreased cardiac output due to heart disease. (43) Therefore, by medically decreasing the systemic resistance, cardiac output is increased and thereby keeps the arterial pressure in the normal range.

When dealing with pathophysiologic alterations of systemic vascular resistance, the distribution of cardiac output is important. The usual methods of measuring cardiac output are useful only in determining overall cardiac output and resistance, and do not delineate the distribution of the flow. It is of obvious importance whether the increased resistance comes mainly from a bed where decreased flow is detrimental, and furthermore, whether the involved bed can compensate for the decreased flow by an increased extraction of oxygen.

Vasoconstriction is actually caused by 3 mechanisms; neural, hormonal, and sodium retention. (11) All of these mechanisms appear to be important. Their relative importance in the individual patient may be related to the type of heart disease. (44)

The arteriolar beds which are most commonly constricted with heart failure are the splanchnic, skeletal muscle, and renal beds. These beds are heavily innervated with sympathetic fibers. Denervation and sympathetic blocking studies indicate that the neural mechanism is important and chiefly works by alpha stimulation. (8, 9, 11, 29, 45)

Angiotensin II is the chief known hormone which causes vasoconstriction in the heart failure state. (16, 36, 46-48) Angiotensin II is a product of renin action and therefore its action is secondary to the factors which cause the secretion of renin. (46) The role of the renin secreting factors in heart failure is not clear, but renin secretion is known to be influenced by renal perfusion pressure, tubular sodium, various hormones, and beta adrenergic stimulation. (46, 49) Other vasoconstrictive hormones have not been shown to have as important an effect on the systemic vasoconstriction in heart failure as Angiotensin II. (11)

Sodium retention and/or vasocongestion have a direct effect on the skeletal muscle vasculature which results in both a decrease in resting flow and flow after vasodilatation. (10, 50) In patients with heart failure and systemic venocongestion, muscle blood flow increases after diuresis. (50) A possible mechanism for systemic arteriolar constriction is venocongestion leading to decreased muscle blood flow, which causes muscle hypoxia, which then stimulates systemic arteriolar constriction. (10)

Regardless of the mechanism, the vascular beds which undergo vasoconstriction secondary to heart failure are the skeletal muscle, splanchnic, and renal beds. (10, 18, 31, 45, 50) The coronary and cerebral beds do not vasoconstrict significantly, and the skin has a variable response due to its need to dissipate heat. (11) The skeletal muscle and splanchnic beds seem to be the most affected.

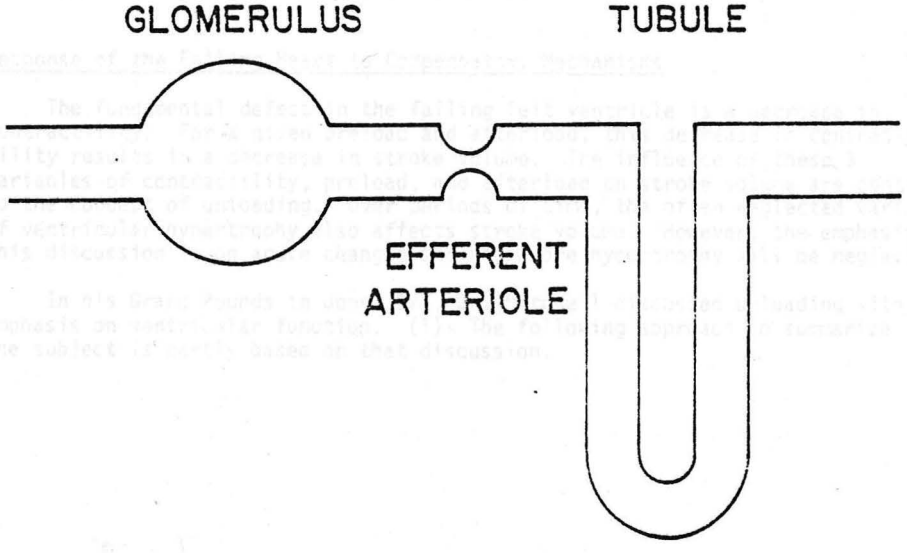
(18, 45, 51, 52) The renal bed is affected somewhat less. However, as heart failure progressively worsens, renal blood flow falls. Presumably because the vasoconstriction is chiefly in the efferent arteriole, glomerular filtration rate does not decrease as much as renal blood flow. However as heart failure worsens, eventually the glomerular filtration rate also falls, leading to an elevation of the BUN and creatinine. At this point, refractoriness to diuretics frequently develops. (17, 47, 53, 54)

During exercise, vasodilatation of the exercising muscle vasculature occurs while vasoconstriction of the nonexercising muscle, splanchnic, and renal beds occurs. (18, 29) The severity of the compensatory vasoconstriction parallels the severity of the heart failure. The flow to the exercising muscle is less than normal. This decreased flow is compensated by an increased oxygen extraction. However in severe states, this increased oxygen extraction is insufficient compensation leading to a net decrease in oxygen delivery. (10)

Preload Response to Heart Failure

The circulation increases preload in response to heart failure by the mechanisms of sodium retention and an increase in venous tone.

Sodium Retention. (14-18, 34) The retention of sodium is followed by a proportionate increase in retention of water and consequently intravascular volume. The mechanism whereby the kidney actually retains sodium is not clearly understood, but the retention is known to be due to increased tubular reabsorption rather than decreased glomerular filtration. The most widely held theory is that the primary event in renal sodium retention is vasoconstriction of the efferent arteriole secondary to direct sympathetic nervous stimulation and/or Angiotensin II. The vasoconstriction is shown diagrammatically below.



The vasoconstricted efferent arteriole decreases renal blood flow, but because the arteriolar constriction is after the glomerulus, glomerular pressure and therefore filtration is preserved. Thus, for any given renal blood flow, the relative amount of glomerular filtrate is increased. This increases the peritubular capillary oncotic pressure while decreasing the peritubular hydrostatic pressure. The net effect is an increase in the tubular reabsorption of sodium.

Other possible sodium retaining influences are increased aldosterone, redistribution of renal blood flow from sodium excreting to sodium retaining nephrons, and poorly characterized intrarenal and extrarenal hormones.

Venous Tone. In addition to an absolute increase in fluid, patients in heart failure frequently have an increase in venous tone. (11, 18, 36) In the skeletal muscle venous bed, the increased tone is probably due to venous congestion. (50, 55) However in the splanchnic venous bed, tone is regulated by the sympathetic nervous system. (18, 56) Since the splanchnic veins contain about 1/4 of the total blood volume, changes in tone of the splanchnic venous bed can be quite important in regulating preload. (18)

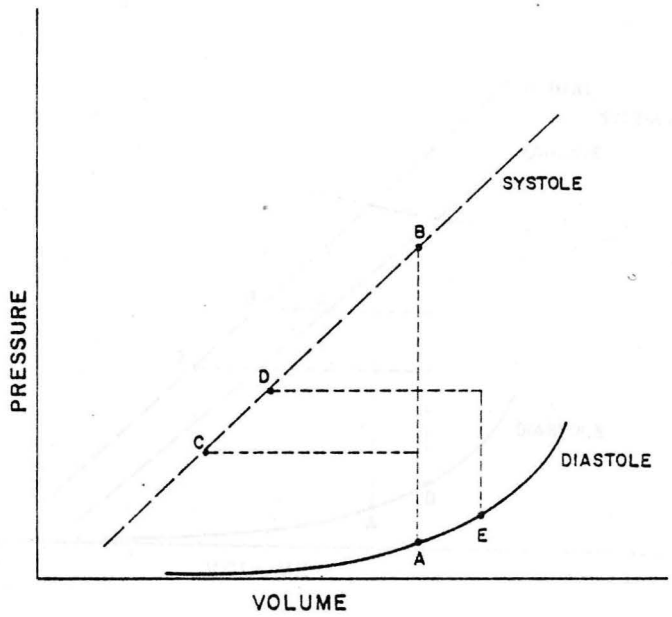
Acute Changes in Venous Tone and Vascular Volume. During periods of acute pulmonary edema, vascular volume is shifted from the peripheral to the pulmonary circuit. This shift is due to an increase in peripheral venous tone and/or decreased left ventricular output. The resulting high pressure in the pulmonary system results in pulmonary edema due to a displacement of hypooncotic fluid from the vascular space into the alveoli. In addition to its obvious detrimental effect on gas exchange, the loss of fluid from the vascular space can sometimes significantly decrease intravascular volume, increase the hematocrit, and increase serum oncotic pressure. (57, 58) Vascular volume can be reduced so much that later in the course of the acute event, apparently after venous tone has relaxed, patients can actually develop shock primarily due to a decreased preload. (59) The clinical point of this chain of events is that patients in pulmonary edema and shock must have their ventricular filling pressure (preload) directly measured.

Response of the Failing Heart to Compensatory Mechanisms

The fundamental defect in the failing left ventricle is a decrease in contractility. For a given preload and afterload, this decrease in contractility results in a decrease in stroke volume. The influence of these 3 variables of contractility, preload, and afterload on stroke volume are central to the concept of unloading. Over periods of time, the often neglected variable of ventricular hypertrophy also affects stroke volume. However, the emphasis in this discussion is on acute changes and therefore hypertrophy will be neglected.

In his Grand Rounds in June 1977, Dr. Mitchell discussed unloading with emphasis on ventricular function. (1) The following approach to summarize the subject is partly based on that discussion.

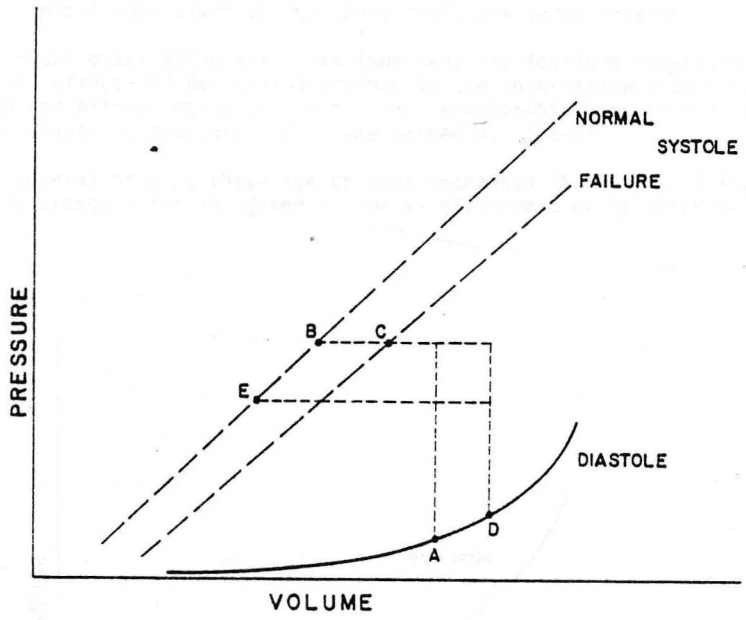
In the diagram below, the relationship between preload, afterload, and stroke volume is explained. (1, 60-62) Contractility is assumed constant.



The diagram illustrates the relationship between left ventricular pressure and volume during diastole (solid line) and systole (dashed line). If diastolic pressure (preload) is sufficient to distend the ventricle to point A and then systole occurs, the volume will change to a point on the dashed line. The point on this line will depend on systolic pressure (afterload). If the systolic pressure is high, then the systolic volume will be high at point B and there will be no change in volume from diastole to systole, i.e. no stroke volume or isovolumic contraction. If the systolic pressure is low, then systolic volume will be low at point C and a large stroke volume will occur. Point D represents intermediate systolic volume and pressure.

The effect of changing preload is illustrated by the same diagram. An important point is that the systolic pressure volume relationship is not affected by the diastolic pressure or volume. If diastolic volume is increased to point E and, as stated, the systolic pressure-volume relationship does not change, then stroke volume will be increased.

If the left ventricle begins to fail, a decrease in contractility is indicated by a shift in the line relating systolic pressure and volume, as shown below:



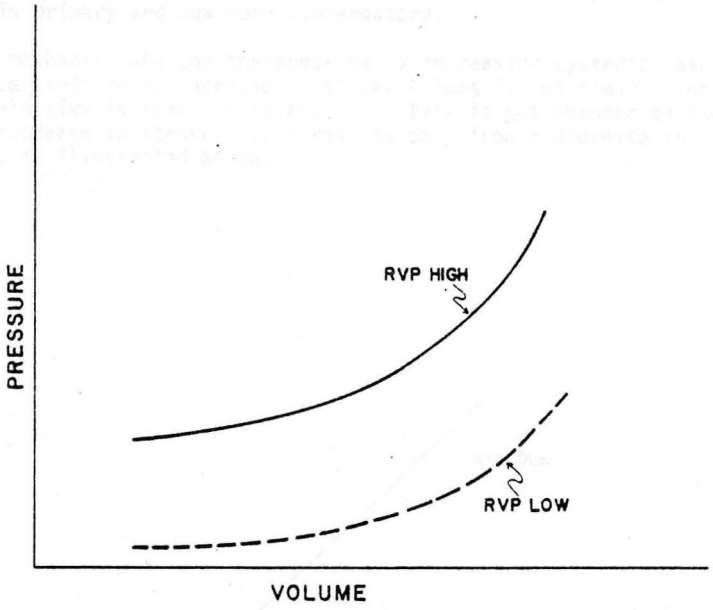
If the ventricle is functioning at point A on the diastolic curve, then the decrease in contractility will change systolic volume from point B to point C, assuming unchanged systolic pressure. Stroke volume will, therefore, decrease from the horizontal distance between A-B to the distance between A-C. To regain stroke volume, either one or both of 2 changes can occur. Diastolic volume and pressure can increase changing the diastolic volume from point A to point D which would increase stroke volume from the horizontal distance between A-C to that between D-C. Alternatively, systolic pressure can decrease changing systolic volume to point E. This would increase stroke volume from the horizontal distance between A-C to that between A-E.

Preload. In the failing ventricle, a high diastolic volume is frequently needed to obtain a sufficient stroke volume. On the other hand, to increase the diastolic volume usually requires increasing the diastolic pressure. This increased diastolic pressure is reflected into the pulmonary veins, and if too high, causes pulmonary edema. Therefore, manipulation of the end diastolic pressure is frequently a two edged sword. Clinical

studies and experience have shown that at a pressure of about 20 mmHg, the diastolic pressure-volume relationship steepens to the point that there is little value in the diastolic pressure being higher. (63-67) Consequently, 20 mmHg is recommended as an approximate upper limit for diastolic pressure, or its clinical equivalent of pulmonary capillary wedge pressure.

A recent observation which has important implications regarding the beneficial effects of decreasing preload is the observation that nitroglycerin and nitroprusside can change the relationship between left ventricular diastolic pressure and volume markedly. (68-71)

In several studies these agents have decreased the left ventricular diastolic pressure for any given volume as diagrammatically shown below.



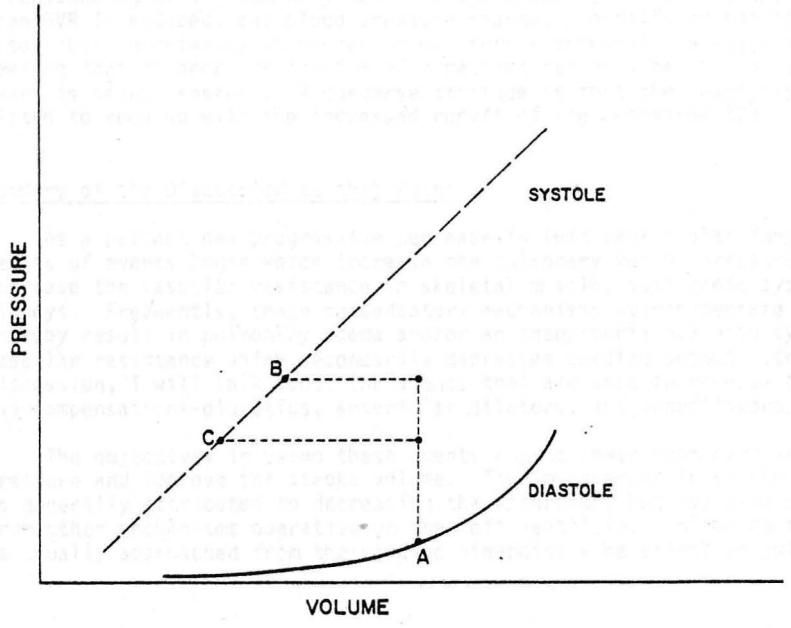
The reason for this shift in the curve is not certain, but is thought to be a decrease in right ventricular pressure and volume. (68, 69) If so, diuretics may have the same effect. The beneficial effects are obvious as diastolic pressure can drop as diastolic volume, and consequently stroke volume, increases.

Systemic Vascular Resistance. The interaction of systemic vascular resistance (SVR), stroke volume (SV), and aortic blood pressure (BP) are shown by the formula below.

$$BP = SV \times HR \times SVR$$

In most cases of heart failure, heart rate (HR) changes little. An overly simplistic concept of the above relationship in heart failure is that SVR increases just as needed to compensate for a diminished stroke volume. However, it is now clear that in most cases of heart failure, a therapeutic decrease in SVR results in an increase in stroke volume as well as a decrease in BP. (43) It is not always clear, however, just how much stroke volume reserve is present, which is why a reduction in SVR should always be approached with caution. The relationship between stroke volume and SVR is, therefore, circular and it is unclear how much of the change in each is primary and how much compensatory.

The mechanism whereby therapeutically decreasing systemic vascular resistance leads to an increase in stroke volume is not clear. The most widely held view is that the contractile state is not changed by therapy and the increase in stroke volume results only from a decrease in systolic pressure, as illustrated below.



The stroke volume in the failure state is represented by the horizontal distance between A-B. If systolic pressure is decreased, then the systolic volume will decrease to C, giving an increase in stroke volume represented by the horizontal distance A-C. However, the results which support this concept are generally taken from studies in which any intrinsic or reflex regulation of the ventricle has been prevented. In these studies, the reflexes are usually blocked and/or the measurements are made on the beat after an abrupt change in pressure, before any intrinsic regulation can occur. (61, 62, 72-76) However, if the measurements are made a few minutes after pressure is changed in the reflex-blocked dog model, stroke volume is independent of systolic pressure. (77-79) In patients, as opposed to these dog models, reflexes are not artifically blocked. The effect of the baroreceptor reflex on ventricular contractility is debated. (62, 79, 80) However, it is possible that this reflex could influence the stroke volume to increase when blood pressure is therapeutically decreased. Another complicating factor is the fact that wall stress, which is the most specific in vivo measure of the load on the myocardial fiber, is dependent on chamber size and wall thickness, as well as pressure. If these ventricular dimensions change, the relationship between systolic pressure and volume may change. Finally, another possible reason for stroke volume increasing is the fact that hydralazine, nitrates, and nitroprusside may either directly improve cardiac function or improve function by improving coronary flow. (81-85)

Whatever the mechanism, the failing heart usually responds to a decrease in SVR with an increase in stroke volume. The mechanism of this effect is important from a clinical standpoint chiefly because it may provide some understanding of the commonly observed phenomenon of stroke volume increasing when SVR is reduced, but blood pressure changes minimally or not at all. Also, this uncertainty of mechanism may temper somewhat the subjective feeling that to decrease the SVR of a patient can only be good because the heart is being "rested". A converse attitude is that the heart may be stimulated to keep up with the increased runoff of the decreased SVR.

Summary of the Discussion to this Point

As a patient has progressive decrease in left ventricular function, a series of events begin which increase the pulmonary venous pressure and increase the vascular resistance in skeletal muscle, splanchnic system, and kidneys. Frequently, these compensatory mechanisms overcompensate and thereby result in pulmonary edema and/or an inappropriately high systemic vascular resistance which secondarily depresses cardiac output. In this discussion, I will talk about the agents that are used to reverse this overcompensation--diuretics, arteriolar dilators, and venodilators.

The objectives in using these agents are to lower pulmonary venous pressure and improve the stroke volume. The improvement in stroke volume is generally attributed to decreasing the afterload, but may also result from other mechanisms operative on the left ventricle. Unloading therapy is usually approached from the cardiac viewpoint--the effect on pulmonary

venous pressure and stroke volume. However, some additional insight can be gained by approaching the therapy from the peripheral viewpoint. Using this approach, the question becomes whether the involved peripheral organs -- skeletal muscle, splanchnic bed, and kidneys -- have decreased flow and whether this decreased flow is detrimental. Furthermore, does the arteriolar dilator in question reverse the pathophysiology in the involved organ? Using this peripheral approach, it is hoped that the heart will react to the vasodilatation with enough cardiac output to both perfuse the organ more adequately and still maintain arterial blood pressure.

In the ensuing discussion, the usual therapeutic agents and the results of their use will be covered.

Agents Most Commonly Used for Unloading

Diuretics - Although frequently not considered in discussions of unloading, diuretics are, nevertheless, the most useful and commonly used unloading agent. The chief mechanism of action is to promote sodium excretion, although furosemide clearly has a venodilatory effect that precedes the onset of sodium excretion. (86) The dosage and side effects of diuretics are well known and reviewed in standard texts. Diuretic resistance was recently reviewed in these Grand Rounds. (17)

Nitrates - The action of nitrates is chiefly to dilate systemic venous capacitance vessels. (87-92) Therefore, their action is chiefly to reduce preload with only a minimal effect on the arterioles. The most useful nitrates for unloading are sublingual isosorbide dinitrate (isordil), oral isosorbide dinitrate, and nitroglycerin ointment. The duration of action is 1-2 hours for sublingual isosorbide dinitrate, about 4 hours for oral isosorbide dinitrate, and about 4 hours for nitroglycerin paste. Equivalent doses are 5-10 mg sublingual isosorbide dinitrate, 20-40 mg oral isosorbide dinitrate, and 1-2 inches of nitroglycerin paste. The usual starting dose of oral isosorbide dinitrate is 10 mg and maintenance usually ranges up to 40 mg every 4-6 hours. Side effects are usually related to dosage and include headache and hypotension. The arterial pO_2 frequently drops about 10 mmHg after giving nitrates. (93) Sudden hypotension and bradycardia after sublingual nitroglycerin has recently been reported. (94)

Hydralazine - Hydralazine is an oral agent that directly relaxes the systemic arterioles. (90-92, 95, 96) Its effect on the venous capacitance is minimal. Therefore, it has been the most commonly used oral agent to reduce afterload. The doses used are somewhat higher than those used to treat hypertension. The starting dose is usually 25-50 mg. Approximately 2/3 of patients will respond to 100 mg or less. As high as 600-800 mg have been used in some patients. (96) The necessary dose is then given every 8-12 hours. In patients not in heart failure tachycardia is common, however tachycardia does not occur in patients with heart failure. (90, 92, 95) The major side effects are headaches, nausea, and vomiting. A lupus like syndrome is known to occur in 10-20% of patients treated for hypertension with 400 mg or more per day. (97) Whether this will be a significant problem in patients treated for heart failure is uncertain.

Prazosin - Prazosin is an oral alpha adrenergic blocker that acts on both resistance arterioles and capacitance veins. (98) The dose varies from .5 to 10 mg every 8 hours. (99, 100) The most troublesome side effect is the first dose phenomenon in which symptoms apparently attributable to orthostatic hypotension appear. (98) A current question regarding prazosin is whether tachyphylaxis occurs. Although studies clearly show that the hemodynamic response to a given dose diminishes after several doses, (101, 102) some response is still present after 2 months. (103) In addition, a beneficial response to exercise is well maintained. This good response is attributed to the alpha blockade properties which may only be manifest with exercise. (101, 103)

Converting Enzyme Inhibitors - Inhibitors of the enzyme which converts Angiotensin I to Angiotensin II are now available in oral (Captopril (SQ14225)) (47, 104) and intravenous (teprotide (SQ20881)) (105-107) forms. The action of these drugs is probably to decrease the level of Angiotensin II although they also inhibit the breakdown of the vasodilator, bradykinin. (108) The dose of Captopril is found by titrating up from 2.5 - 5 mg each 1/2 hour. The usual daily dose is 50-300 mg in 2-3 doses. Teprotide is given as a slow intravenous bolus of .25 - 1.0 mg/kg. Its effects last for at least 5-6 hours. Evaluation of these drugs are in the preliminary stages and information as to side effects is scant. In one study 2/10 patients on Captopril developed profound bradycardia and hypotension. (104)

Nitroprusside - Nitroprusside has a direct relaxing effect on vascular smooth muscle. (88-90, 109, 110) It affects arteries and veins approximately equally, therefore, it is considered a reducer of both preload and afterload. In actual practice, it is the most common intravenous agent to lower afterload since phentolamine is expensive and cumbersome to use. Nitroprusside is given by continuous intravenous infusion at a starting dose of .25 µg/kg/min. Maintenance dose averages about 35-120 µg/min, but rates up to 400 µg/min have been used. As with the nitrates, nitroprusside causes an approximate 10 mmHg drop in arterial pO_2. (111, 112) The most serious side effect is the accumulation of thiocyanate, a metabolite of nitroprusside. Thiocyanate levels (toxic > 10 mg/100 ml) should be monitored if the dose is high or use prolonged. (109) Nitroprusside should be discontinued slowly as rebound worsening of the hemodynamic situation may occur. (113)

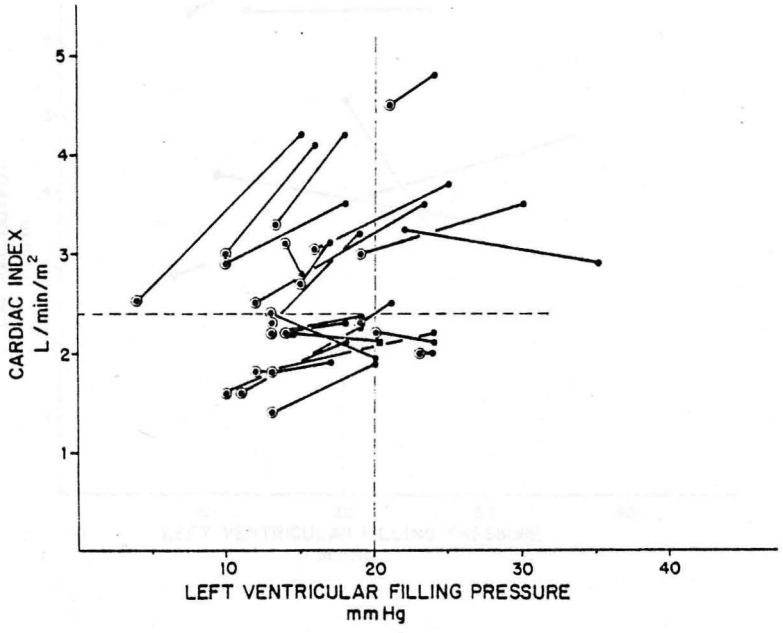
Caution About Side Effects. In the individual discussion of drugs, side effects have often been implied to be minimal. However, the major "side effect" with all of these drugs is an exaggeration of their therapeutic effect. Consequently, hypotension and/or other hemodynamic deterioration is a constant threat. The administration of these drugs, especially in the marginally compensated patient with heart failure should never be undertaken lightly.

Treatment of High Preload

Clinically, the term preload is generally used to indicate left ventricular filling pressure. Preload is most precisely measured by direct catheterization of the left ventricle. The next best measurement is the pulmonary capillary

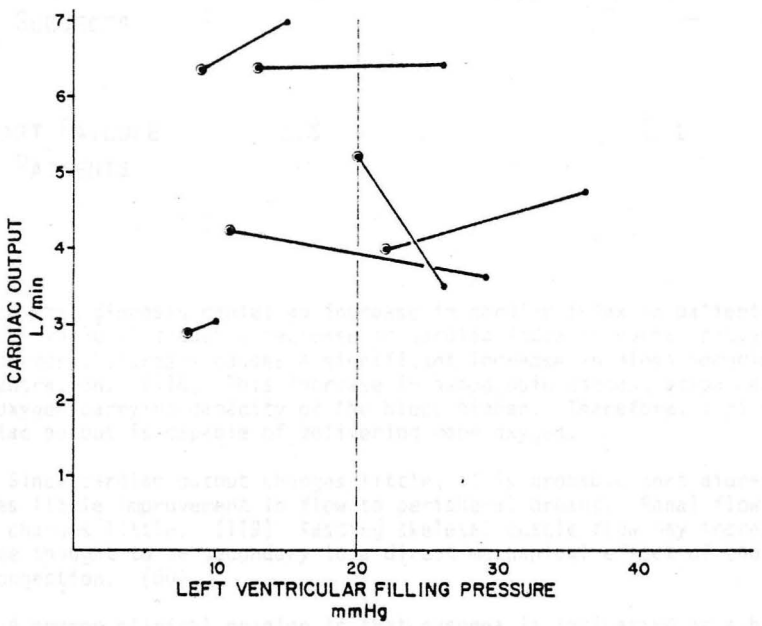
wedge pressure. The third best approximation is the pulmonary artery diastolic pressure. The upper limit of normal for preload is 12 mmHg. In heart failure, an upper limit of 20 mmHg is generally considered appropriate. Preload can be therapeutically reduced by diuresis, venodilatation, or reduction of afterload.

Diuresis. Diuresis is the oldest and most commonly used form of preload reduction in patients with chronic heart failure. Both clinically and by direct measurement, diuresis dramatically reduces preload. Less well known is the effect preload reduction has on cardiac output. There is a general feeling that diuresis reduces cardiac output significantly. Hence, in some patients with high preload and possible low cardiac output, diuretics have been withheld for fear of precipitating low output. However, it appears that patients with low cardiac output and high preload generally respond to diuresis by minimal change or even an increase in cardiac output, as illustrated by the graph below.



The points in this diagram are taken from 2 studies of patients with acute left ventricular failure after myocardial infarction. (114, 115) The ■ points are the mean values of another study of left ventricular failure after infarction. (86) The lines connect points before and after diuresis. Dotted lines indicate approximate limits for desirable filling pressure and cardiac index. Patients whose cardiac output drops after diuresis generally either have low preloads or high cardiac indexes. (Cardiac index = cardiac output/body surface area).

Notice that patients with high preloads and low cardiac indexes generally change their cardiac indexes little with diuresis. The studies in the above diagram were all done on patients in failure after an infarction. Less information is available on patients in chronic heart failure, probably because diuretics were chiefly introduced and studied before bedside catheterization of the pulmonary artery was commonly done. However, the diagram below shows the results of a small study on patients in chronic heart failure. (116)



The vertical axis on this graph is cardiac output instead of index. However, the same trend holds. Patients with a high preload did not drop their cardiac output after diuresis. Finally, one other study in which subjects were separated depending on whether evidence of pulmonary congestion was absent or present is shown on the chart below. (117)

CARDIAC INDEX

L/MIN/M^2

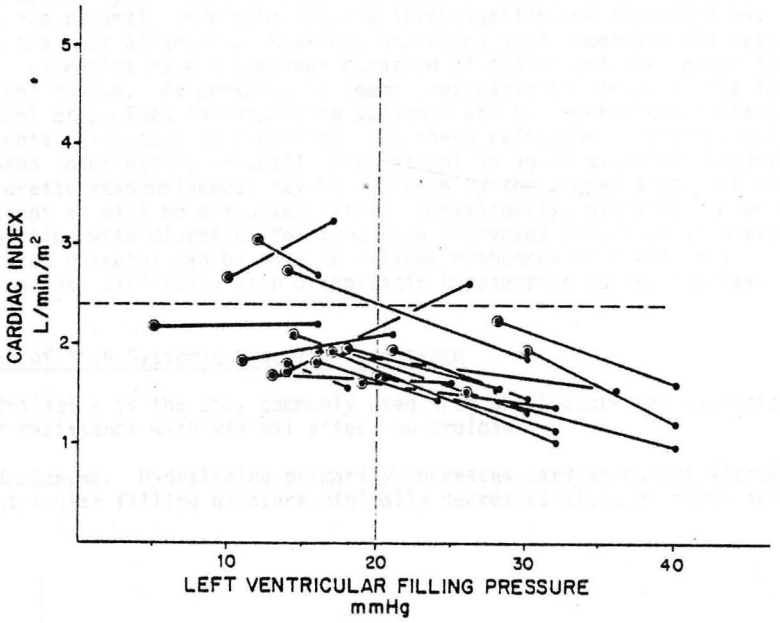
	BEFORE DIURESIS	AFTER DIURESIS
NORMAL SUBJECTS	2.6	2.3
HEART FAILURE PATIENTS	1.8	2.1

Notice that diuresis causes an increase in cardiac index in patients in failure while it causes a decrease in cardiac index in normal patients. Furthermore, diuresis causes a significant increase in blood hemoglobin concentration. (118) This increase in hemoglobin concentration makes the oxygen carrying capacity of the blood higher. Therefore, a given cardiac output is capable of delivering more oxygen.

Since cardiac output changes little, it is probable that diuresis causes little improvement in flow to peripheral organs. Renal flow probably changes little. (119) Resting skeletal muscle flow may increase, a change thought to be secondary to a direct mechanical effect of the relief of congestion. (50)

A common clinical opinion is that dyspnea is indicative of a high preload and that fatigue and decreased exercise tolerance are indicative of a decreased cardiac output. However, in one study, patients were diuresed to a lower preload. Both at rest and at exercise, their cardiac output was lower. However, the patients exercised longer before the onset of fatigue and subjectively felt stronger. (118) Thus, much confidence in the clinical history to diagnose poor output in the face of pulmonary congestion is probably not warranted.

Nitrates. A representative study of the effect of nitrates in patients with chronic left ventricular failure is shown below. (120)



In this study mean heart rate did not change and mean arterial pressure decreased 9%. Numerous studies substantiate these results. (91, 121-126) Notice that a decrease in left ventricular filling pressure is usually attended by an increase in cardiac index, especially when the initial filling pressure is high. All patients do not respond to nitrate therapy. Massive peripheral edema seems to prevent a nitrate response. (127) Most studies have dealt with the acute effects of nitrates, but these effects have been shown to be sustained for up to 3 months. (128-130)

The organs which receive the increased cardiac output are not certain, but occasional increases in urine output after nitrate administration suggest some renal effect. (124) Echocardiographic determination of cardiac dimensions shows no significant change after 8 weeks of therapy. (129)

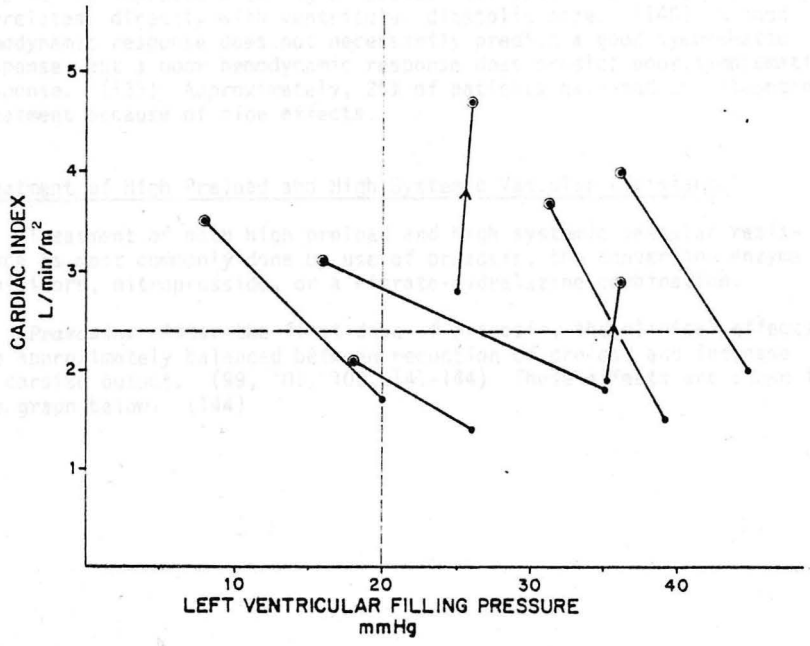
Patients are clearly symptomatically improved, chiefly as a result of relief of dyspnea. Exercise tolerance does not change, although studies at submaximal rates of exercise show improved hemodynamics. (131, 132)

Choice of Therapy for Relief of Preload. Chronic reduction of preload can be attained by diuresis or venodilatation with nitrates. The effect of nitrates has recently undergone intense investigation and therefore has received the most attention. However, diuretics have undergone the test of time. Diuretics have a smoother duration of action and are easier for the patient to use. At present, it seems preferable to use diuretics for the control of preload in responsive patients and to reserve the nitrates for patients refractory to diuretics. In these refractory patients, nitrates can be used indefinitely or until the patient is again diuretic-responsive. (53) Diuretic responsiveness may be achieved by the proper afterload reducing agent as will be discussed later. Occasionally, nitrates can be used in conjunction with diuretics for temporary increased reduction of preload. For example, nitrates can be used to relieve orthopnea at night in a patient who has difficulty with orthostatic hypotension during the day.

Treatment of High Systemic Vascular Resistance

Hydralazine is the only commonly used drug which decreases systemic vascular resistance with minimal effect on preload.

Hydralazine. Hydralazine primarily increases cardiac output although left ventricular filling pressure minimally decreases also, as shown below. (95)



The connected points are before and after oral hydralazine. The higher cardiac indexes are all after hydralazine. These points are from one study, but similar results are found in other studies. (91, 133-135) In these studies, hydralazine does not change the heart rate and decreases mean blood pressure 0 - 12%.

Blood flow at rest is increased to the forearm by 41%. (95) Although this presumably means that blood flow to resting skeletal muscle is increased, the objectively measured exercise tolerance is not increased. (136) Lactate levels during exercise are not changed by hydralazine. (136) Since hydralazine increases cardiac output during exercise, (135-137) the presumed physiology is that hydralazine increases flow to organs other than exercising muscle. An additional possibility for the lack of improvement in exercise tolerance is that left ventricular filling pressure during exercise is unchanged by hydralazine. (137)

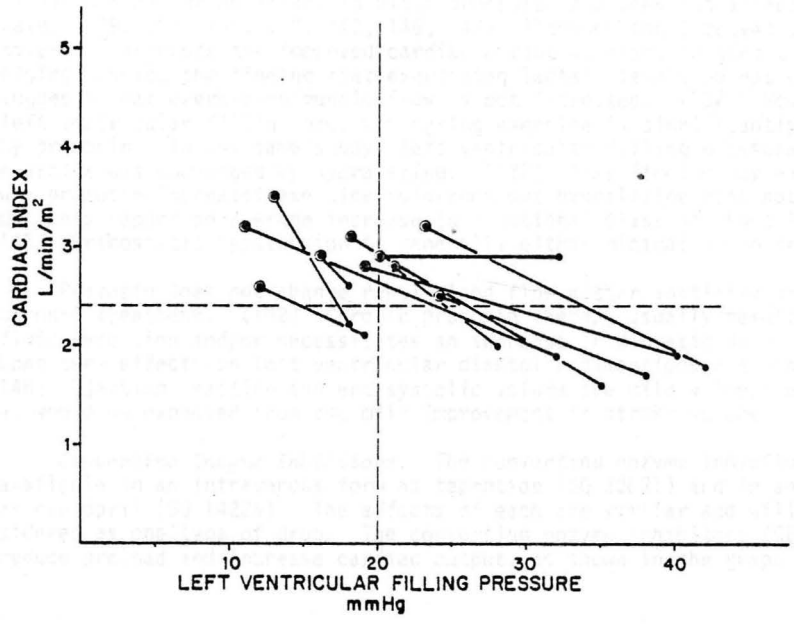
In the patient with severe heart failure hydralazine increases renal blood flow by 127%, glomerular filtration by about 10%, and sodium excretion slightly. (137, 138) Clinically, little change in diuretic responsiveness is found, (139) although sporadically, hydralazine may decrease (139, 140) or increase diuretic responsiveness. (53, 140)

Although objective evidence of improvement in an individual's function is hard to document, approximately 60% of patients report an improvement of at least one functional class. (139) This response rate may be improved with higher doses. Clinical responsiveness correlates directly with ventricular diastolic size. (140) A good hemodynamic response does not necessarily predict a good symptomatic response, but a poor hemodynamic response does predict poor symptomatic response. (139) Approximately, 25% of patients have had to discontinue treatment because of side effects.

Treatment of High Preload and High Systemic Vascular Resistance

Treatment of both high preload and high systemic vascular resistance is most commonly done by use of prazosin, the converting enzyme inhibitors, nitroprusside, or a nitrate-hydralazine combination.

Prazosin. After the first dose of prazosin, the clinical effects are approximately balanced between reduction of preload and increase in cardiac output. (99, 101, 102, 141-144) These effects are shown in the graph below. (144)



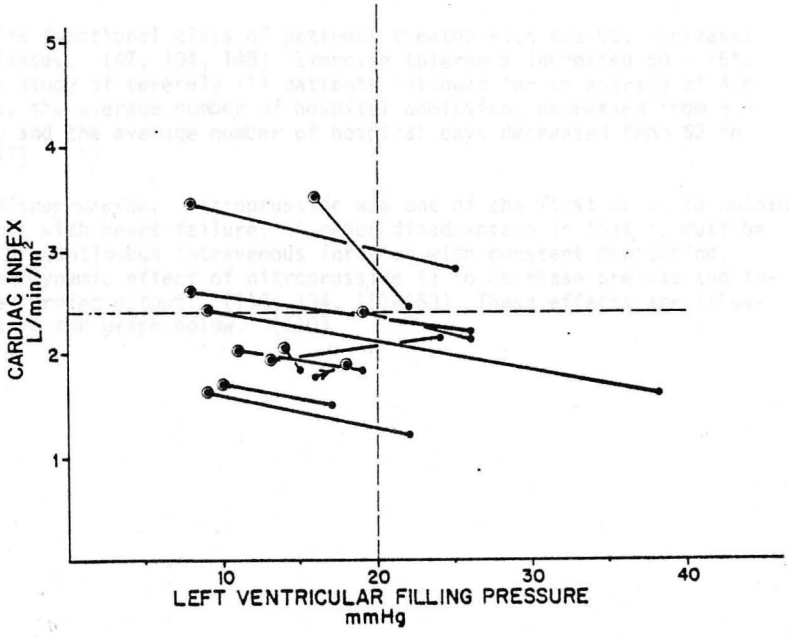
The blood pressure drops an average of 10% while the mean heart rate does not change. Because of prazosin's balanced effects on preload and afterload, minimal side effects, and ease of administration; it was initially felt to be an ideal agent for the treatment of the hemodynamic abnormalities of severe heart failure at rest. However it was soon found that a marked attenuation of the drug's hemodynamic effects occurred as soon as the third to fifth dose. (101, 102, 142, 145). By the fifth dose, most of the improvement in the cardiac index and left ventricular filling pressure is gone, although the decrease in aortic pressure remains. These findings obviously were discouraging to the long term use of prazosin.

However, recently the exercise capacity of patients on long term prazosin has been shown to be improved by 29 - 70%. (99, 103, 143, 146, 147) This increase in exercise tolerance is consistent with the observation that prazosin has a relatively greater effect on exercise hemodynamics than on resting hemodynamics. (136) The presumptive reason for this relatively greater effect during exercise is that prazosin is an alpha adrenergic blocker and alpha adrenergic activity becomes more prominent during exercise. The specific hemodynamic reason for the improved exercise tolerance is not

certain. During exercise, prazosin chiefly improves stroke volume, has either minimal or no effect on blood pressure, and does not affect heart rate. (99, 103, 136, 137, 143, 146, 147) Although the improved exercise tolerance suggests the improved cardiac output at exercise goes to exercising muscle, the finding that exercising lactate levels do not change suggests that exercising muscle flow is not increased. (137) However the left ventricular filling pressure during exercise is significantly decreased by prazosin. In the same study, left ventricular filling pressure during exercise was unchanged by hydralazine. (137) This finding may explain why prazosin increases exercise tolerance but hydralazine does not. Overall, patients report an average increase in functional class of about 1.5. (103, 143) Orthostatic hypotension is generally either minimal or no problem.

Prazosin does not change renal blood flow either initially or after chronic treatment. (102) Chronic prazosin therapy usually results in mild fluid retention and/or necessitates an increase in diuretic dose. (103, 147) Long term effects on left ventricular diastolic dimensions are minimal. (103, 146) Ejection fraction and end systolic volume are mildly improved, (103, 146) as would be expected from the mild improvement in stroke volume.

Converting Enzyme Inhibitors. The converting enzyme inhibitors are available in an intravenous form as teprotide (SQ 20881) and in an oral form as captopril (SQ 14225). The effects of each are similar and will be considered as one type of drug. The converting enzyme inhibitors (CEI) both reduce preload and increase cardiac output, as shown in the graph below. (148)

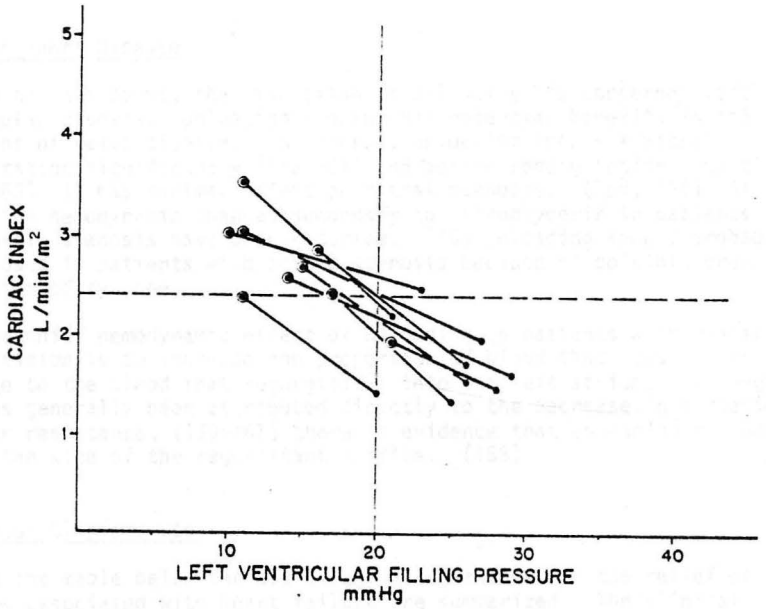


Because of general acceptance of the fact that the effect of Angiotensin II is on the resistance arterioles, it is surprising how much the CEI reduce preload. (104) The points in the above graph are from one study, (148) but other studies show similar results. (47, 104-107, 149) The arterial pressure in these studies is decreased acutely by 10 - 25%, and results vary as to whether the pressure goes back up with chronic administration. (104, 148) Heart rate changes little, but tends to decrease. The hemodynamic effects seen with acute administration persist with chronic administration. (104) Side effects seem to be few, but occasionally bothersome hypotension and bradycardia develop after the first dose. (104) Results are conflicting as to whether the response to the CEI can be predicted from the plasma renin activity. (105, 107, 148) The correlation between renin activity and response is best when patients with very high plasma renin activities are studied. (148)

As opposed to the other afterload reducing agents, the CEI have a definite salutary effect on renal function. Renal blood flow is increased, glomerular filtration is increased, and probably most importantly, sodium excretion is increased. (47) The diuretic effect is especially dramatic in those patients refractory to conventional diuretics. (47) Patients severely ill with heart failure lose an average of 4 kg in the week after beginning treatment. (47) Blood flow to skeletal muscle is not increased when cardiac output is increased, implying preferential flow to other organs. (105) A dog model study in which renin activity was induced by volume depletion was consistent with the effect of the CEI to increase flow to the kidneys while decreasing flow to skeletal muscle. (150) Objective evidence of significant improvement in cardiac function is scant, but one study showed a mild improvement in the cardiothoracic ratio. (148)

The functional class of patients treated with the CEI increases 1-2 classes. (47, 104, 148) Exercise tolerance increased 50 - 75%. In one study of severely ill patients followed for an average of 4.6 months, the average number of hospital admissions decreased from 3.8 to .5, and the average number of hospital days decreased from 62 to 5. (47)

Nitroprusside. Nitroprusside was one of the first drugs to unload patients with heart failure. A major disadvantage is that it must be given by continuous intravenous infusion with constant monitoring. The hemodynamic effect of nitroprusside is to decrease preload and increase cardiac output. (110, 134, 151-153) These effects are illustrated in the graph below. (110)



Mean arterial pressure usually is decreased 10 - 15 mmHg when the above changes occur. Heart rate does not change. When nitroprusside is given for short periods, side effects are minimal, but the potential for overdosage and consequent dangerous hypotension is ever present.

Renal blood flow is moderately increased (134) while glomerular filtration tends to improve either minimally, (151) or not at all. (134) In one study, sodium excretion did not increase. (134) However, in another study with very sick patients, nitroprusside markedly improved sodium excretion and was felt to initiate diuresis in some patients previously resistant to conventional diuretics. (151) Forearm blood flow increases moderately. (153)

Patients are felt to symptomatically improve after nitroprusside infusion. However, objective documentation is difficult because of their nonambulatory state.

Hydralazine - Nitrate Combination. In an attempt to simulate the balanced venous arterial effects of nitroprusside in an oral form, the combination of hydralazine and nitrates has been used. As expected, the hemodynamic effects of this combination are the preload reducing effect of the nitrates and the systemic vascular resistance reducing effect of hydralazine. (154-156) Exercise capacity is not increased by this combination. (157)

Valvular Heart Disease

Up to this point, the discussion of unloading has concerned left ventricular disease. Unloading therapy has potential benefits in the treatment of valve disease. In general, unloading improves mitral regurgitation significantly (158-161) and aortic regurgitation modestly. (162, 163) It has minimal effect on mitral stenosis. (164, 165) Although the hemodynamic changes secondary to nitroglycerin in patients with aortic stenosis have been reported, (166) unloading should probably not be used in patients with aortic stenosis because of possible precipitation of syncope.

The chief hemodynamic effect of unloading in patients with mitral regurgitation is to increase the proportion of blood that goes forward relative to the blood that regurgitates into the left atrium. Although this has generally been attributed directly to the decrease in systemic vascular resistance, (159-161) there is evidence that unloading may decrease the size of the regurgitant orifice. (158)

Summary of Clinical Use

In the table below the use of unloading agents for the relief of problems associated with heart failure are summarized. The clinical conditions are generally listed from top to bottom as progressively worse problems.

Problem	Diuretic	Nitrate	Hydralazine	Nitro Prusside	Prazosin	Converting Enzyme Inhibitor
Congestion Diuretic Responsive	‡	‡	+	‡	+	+
Exercise Tolerance Diuretic Responsive	‡	‡	+	+	‡	‡
Diuretic Resistance	+	+	‡	‡	+	‡
Congestion Diuretic Resistant	+	‡	+	‡	+	‡
Exercise Tolerance Diuretic Resistant	+	‡	+	+	‡	‡

\+ Poor ‡ Best

The patients who present with only pulmonary congestion and are responsible to diuretics should first be diuresed. Nitrates have little use in this condition on a chronic basis, but may be used in patients who need transient reversible reductions in preload, such as for sleep. Exercise tolerance is generally improved in patients by reduction of preload and relief of congestion. However, if further improvement in exercise tolerance is desired, prazosin may be tried. If this additional agent is used, preload should be on the high rather than low side (approximately 20 - 24 mmHg) prior to its use to avoid the additive effect with the diuretic, which could result in too low a preload. The effect of prazosin can be measured by exercise testing.

In patients who are resistant to diuretics, hydralazine and/or nitroprusside may restore responsiveness. After responsiveness is restored, they may or may not be needed to maintain responsiveness. The converting enzyme inhibitors appear to be superior agents to restore responsiveness. While awaiting diuresis, the nitrates or nitroprusside may be used to lower preload, although severely edematous patients frequently do not respond to nitrates. The converting enzyme inhibitors also reduce preload directly, in addition to their diuretic effect. Relief of congestion in these patients generally improves exercise tolerance.

In patients who are severely ill, all of the unloading agents give symptomatic relief. If this relief is the result of a decrease in pulmonary congestion, restoration of diuretic responsiveness, or a documented increase in exercise tolerance; the relief in symptoms is easily understandable. However, some agents, such as hydralazine, result only in an increase in cardiac output, and a sense of "feeling better". The increased cardiac output has not been shown to be going to a vital organ. In this situation it is difficult to say whether the overall patient is improved, or the increased flow is giving a false sensation of improvement. Conceivably, the latter could result from increased skin or resting muscle flow.

All patients who are being begun on unloading therapy should be hospitalized with the possible exception of mildly ill patients being started on diuretics. Cardiac output and left ventricular filling pressure should be measured in patients receiving hydralazine, nitroprusside, and the converting enzyme inhibitors. This pressure-output monitoring is necessary to determine for certain that the patient's hemodynamic situation is suitable for unloading, to monitor the dose, and to document response to the drug before putting the patient on a chronic regimen. Prazosin can best be monitored with exercise tests, although the patient should be closely observed after the first doses.

Although there is much investigation yet to be done, my present opinion is that patients should be treated with these unloading agents only for the relief of symptoms. There is no evidence that use of these agents in the treatment of heart failure improves longevity except as they improve symptoms.

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