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AFTERLOAD REDUCTION IN THE TREATMENT OF HEART DISEASE: ITS PHYSIOLOGICAL MEANING AND CLINICAL APPLICATION

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MEDICAL GRAND ROUNDS

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I. Introduction

II. Physiological Meaning of Afterload Reduction

A. Cardiac Muscle Mechanics

1. Method of Study and Definitions
2. Effect of Preload, Contractile State and Afterload

B. Left Ventricular Mechanics

1. Definitions
2. Effect of End-Diastolic Volume (Preload), Contractile State, and Resistance to Ejection (Afterload)

C. Myocardial Energetics

D. Concept of Afterload Reduction Therapy in Heart Disease

III. Clinical Methods of Afterload Reduction

A. Arterial Counterpulsation

B. Vasodilator Drugs

1. Effect on systemic resistance and capacitance vessels
2. Possible complications of vasodilator therapy

IV. Applications of Afterload Reduction Therapy

A. Acute Myocardial Infarction with Left Ventricular Failure

1. Hemodynamic Effects
2. Effect on Size of the Myocardial Infarction
3. Long-term Prognosis

B. Refractory Chronic Left Ventricular Failure

C. Valvular Disease

1. Mitral Regurgitation
2. Aortic Regurgitation

D. Cardiac Tamponade

V. Conclusions

I. Introduction

1. Mitchell JH, Hefner LL, Monroe RG: Performance of the left ventricle. Am J Med 53:481, 1972.

2. Cohn JN: Vasodilator therapy for heart failure. The influence of impedance on left ventricular performance. Circulation 48:5, 1973.

3. Chatterjee K: Vasodilator therapy for heart failure. Ann Int Med 83:421, 1975.

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Effective performance of the left ventricle requires the maintenance of a cardiac output as demanded by the systemic circulation without a high hemodynamic cost or pressure in the pulmonary capillary bed and without a high metabolic cost or oxygen demand by the left ventricular myocardium. Traditionally the performance of the failing left ventricle has been considered in terms of its diastolic filling, the Frank-Starling mechanism, and its contractile state. Only recently has the role of the resistance to ejection or arterial impedance been appreciated in the treatment of left ventricular failure.

The principal consequences of left heart failure are related to a reduced cardiac output in relation to the needs of the systemic circulation and an elevated left ventricular filling pressure. The former "forward failure" results in easy fatigability in its mildest form and cardiogenic shock in its severest form and the latter "backward failure" in pulmonary congestion with ensuing dyspnea, orthopnea and paroxsymal nocturnal dyspnea. Therapy for "forward failure" of the left ventricle has been positive inotropic agents (digitalis and β-adrenergic receptor stimulating drugs) and for "backward failure" has been diuretics, IPPB, rotating tourniquets, and phlebotomy.

With the decreased cardiac output in left heart failure, there is a reflexly induced increase in systemic vascular resistance in an attempt to maintain arterial pressure within normal or near normal range. This intrinsic compensatory mechanism is actually detrimental since it may further reduce cardiac output by increasing the afterload on the failing left ventricle. Relief of this increase in afterload has caused improvement in patients with various types of heart disease.

The purpose of this Grand Rounds is to review cardiac muscle and left ventricular mechanics, emphasizing the effects of afterload or resistance to ejection, and to review myocardial energetics. Next, the clinical methods of afterload reduction will be discussed and finally an appraisal will be made of the current status of afterload reduction in the treatment of heart disease.

II. Physiological Meaning of Afterload Reduction

A. Cardiac muscle mechanics

1. *Loc Cit*

4. *Loc Cit*

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8. Mitchell JH, Wildenthal K: Problems in measurement of myocardial contractility. Proc Roy Soc Med 65:6, 1972.

9. Brutsaert DL, Sonnenblick EH: Cardiac muscle mechanics in the evaluation of myocardial contractility and pump function: Problems, concepts, and directions. Prog Cardiovas Dis 16:337, 1973.

10. Abbott BC, Mommaerts WFHM: A study of inotropic mechanisms in the papillary muscle preparation. J Gen Physiol 42:533, 1959.

11. Sonnenblick EH: Force-velocity relations in mammalian heart muscle. Am J Physiol 202:931, 1962.

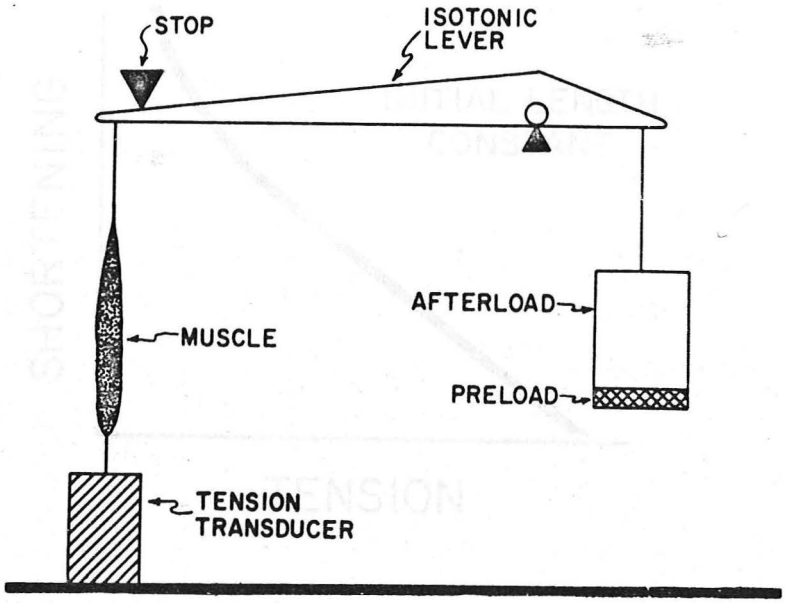
12. Sonnenblick EH: Determinants of active state in heart muscle: force, velocity, instantaneous muscle length, time. Fed Proc 24:1396, 1965.

13. Taylor RR: Active length-tension relations compared in isometric, afterloaded, and isotonic contraction of cat papillary muscle. Their dependence on inotropic state. Cir Res 26:279, 1970.

1. Methods of Study and Definition

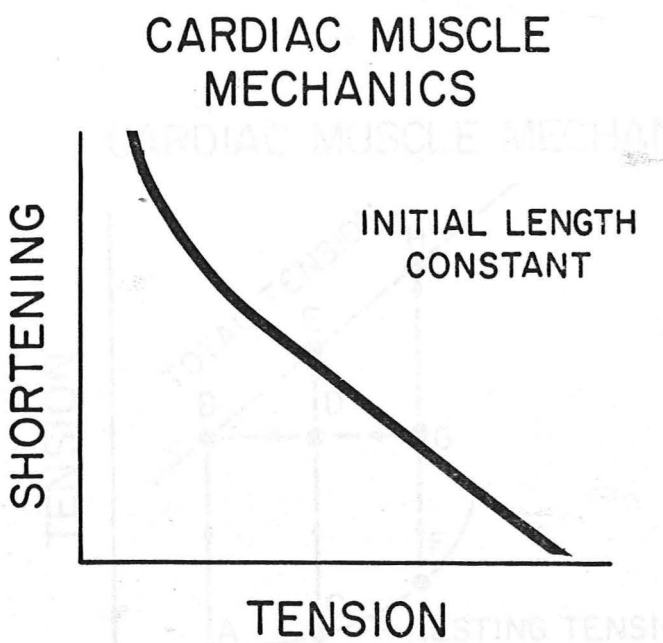
Much work has been done recently on the mechanics of cardiac muscle contraction. An attempt has been made to apply the concepts which have been well worked out for skeletal muscle to cardiac muscle. Even though there are many theoretical problems involved with this approach, much useful information has been derived from such an analysis.

Figure 1



An experimental arrangement for studying cardiac muscle is shown in Figure 1. One end of a cat papillary muscle is attached to a transducer for measuring tension and the other to an isotonic lever for measuring length changes. The initial length of the muscle is set by a preload, and is then held constant by fixing a stop above the isotonic lever. An added load, afterload, is not encountered by the muscle until it attempts to shorten. The total load is the preload added to the afterload.

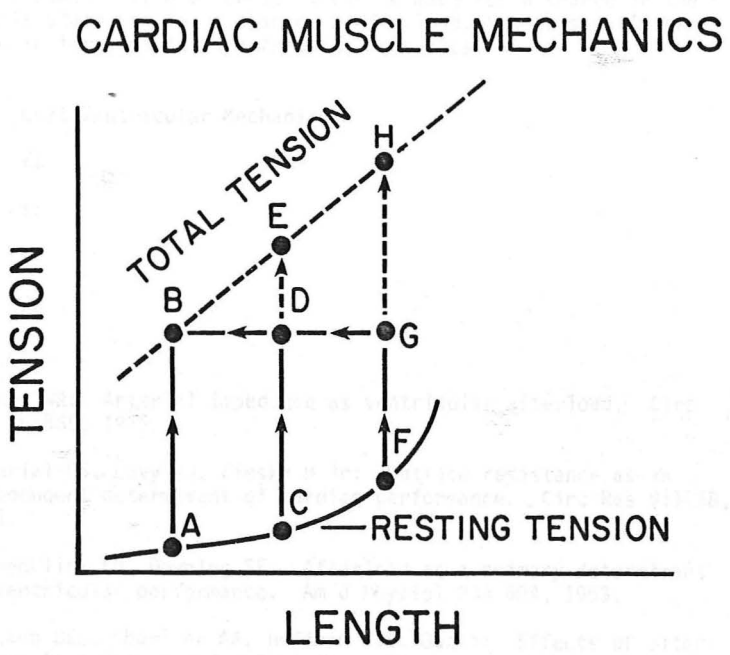
Figure 2



If the total load is greater than the muscle is capable of lifting, then an isometric contraction occurs and the muscle only develops tension. If the total load is less than the tension developing capabilities of the muscle, then an isotonic contraction occurs and the muscle shortens after it develops the required tension. Thus, when cardiac muscle goes from the resting to the contracted state it has the potential to develop force and to shorten. The course of the contraction is actually determined by the external restraints which are imposed. This fact is shown in Fig. 2 where the amount of shortening is plotted against the tension. The preload or initial length of the muscle is held constant. The afterload is set so that the total load (preload + afterload) is just great enough that the muscle is unable to shorten. Under this imposed restraint the muscle develops its maximal amount of tension (isometric contraction). If the afterload is progressively decreased the amount of shortening increases and the tension development decreases (isotonic contractions). When the afterload is removed and the total load is equal to the preload, the amount of shortening is maximal and the tension development is minimal.

2. Effect of Preload, Contractile State and Afterload

Figure 3



The relationship between the ability of cardiac muscle to develop tension and to shorten is fundamental to an understanding of cardiac muscle mechanics. In Fig. 3 tension is plotted during both rest and the contracted state of the muscle against the length of the muscle fiber. The bottom solid curve is the resting length-tension curve. The upper dashed line is the total tension that would be attained during an isometric contraction. The developed tension is the difference between the total tension and the resting tension. At a short muscle length (A) the contraction is isometric and only tension is developed (B). At a longer muscle length (C) the muscle has the potential to develop a higher tension (E). However, if it is only allowed to attain the same total tension as that attained at the lesser length (A), then the muscle will

shorten from D to B. At an even longer muscle length (F), more shortening will occur if the muscle is again only allowed to attain the same tension as the two previous contractions.

By such an analysis one can easily see the effects of increasing resting length, or preload, which is the well known Frank-Starling effect. A similar type of analysis can be made for a change in the contractile state and for a change in afterload, but these will be explained in terms of left ventricular mechanics.

B. Left Ventricular Mechanics

1. *Loc Cit*

4. *Loc Cit*

7. *Loc Cit*

8. *Loc Cit*

9. *Loc Cit*

14. Milnor WR: Arterial impedance as ventricular afterload. Circ Res 36:565, 1975.

15. Imperial ES, Levy MN, Zieske H Jr: Outflow resistance as an independent determinant of cardiac performance. Circ Res 9:1148, 1961.

16. Sonnenblick EH, Downing SE: Afterload as a primary determinant of ventricular performance. Am J Physiol 204:604, 1963.

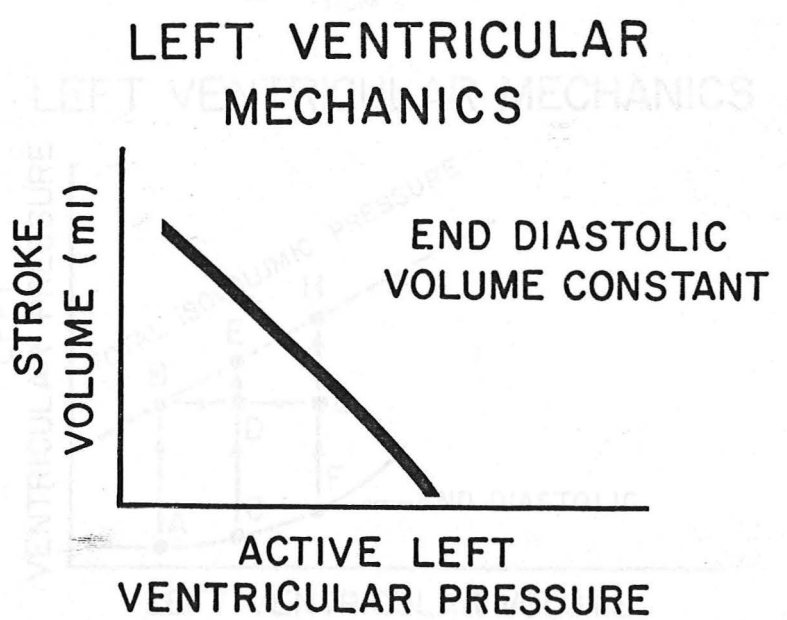
17. Wilcken DEL, Charlier AA, Hoffman JIE, Guz A: Effects of alterations in aortic impedance on the performance of the ventricles. Circul Res 14:283, 1964.

1. Definitions

The concepts which have been derived from cardiac muscle mechanics can be translated into the intact left ventricle. Instead of a shortening-tension relation or a length-tension diagram, as was used to describe the behavior of cardiac muscle, the mechanics of the left ventricle can be depicted in terms of a stroke volume - active left ventricular pressure relation or a left ventricular volume - pressure diagram. The initial fiber length or preload of the left ventricle is the end-diastolic volume. The term afterload which is simply defined for cardiac muscle is a much more complicated concept for the contracting left ventricle.

A strict translation would be the stress faced by the cardiac muscle in the wall of the left ventricle during ejection. Calculation of this entity would include intraventricular pressure, ventricular size and shape (Laplace relation) and wall thickness which are all changing during ejection. A more comprehensible method for dealing with the resistance to ejection is to consider it as the arterial impedance during the movement of the stroke volume into the aorta. Arterial impedance can be defined loosely for hemodynamic use as the instantaneous relation between pressure and flow during ejection. In a strict hydraulic sense it is a much more complex entity involving a series of harmonics that describe pressure and flow. For clinical purposes, however, systemic vascular resistance may be used as an index of arterial impedance. Finally, the contractile state of the left ventricle is analogous to the contractile state of cardiac muscle and is a useful concept although again difficult to define precisely.

Figure 4



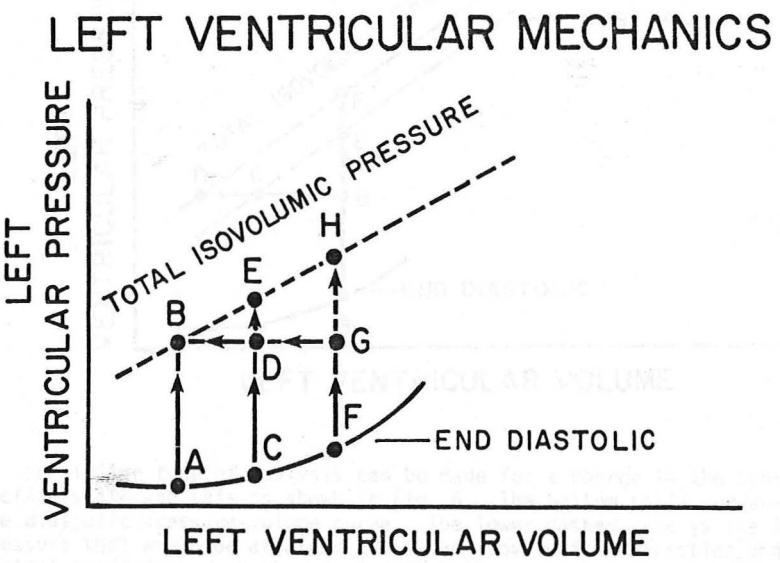
When the left ventricle goes from diastole to systole, it has the potential to develop pressure and to eject volume. So, just as with cardiac muscle, the course of the contraction is determined by the external restraints which are imposed. This is illustrated in Fig. 4

where the amount of stroke volume ejected is plotted against the total pressure attained by the left ventricle during systole. The end diastolic volume (preload) is kept constant. If the aorta is clamped so that no volume can be ejected, then the contraction is isovolumic and the maximal amount of pressure will be developed. As the aortic clamp is progressively released (afterload reduced), the amount of stroke volume ejected increases as the pressure attained decreases. If the aorta is severed, then the stroke volume ejected is maximal and the pressure developed by the left ventricle is minimal.

2. Effect of End-Diastolic Volume (Preload), Contractile State, and Resistance to Ejection (Afterload).

The three determinants of left ventricular mechanics are end-diastolic volume (preload), contractile state, and resistance to ejection (afterload).

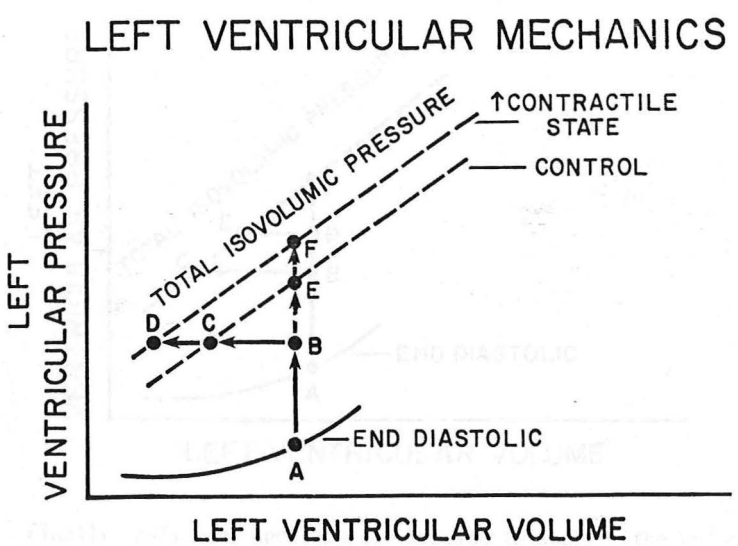
Figure 5



The effect of varying end-diastolic volume or preload on left ventricular mechanics is shown in Fig. 5 where left ventricle pressure is plotted against left ventricular volume. The bottom solid curve is the diastolic pressure-volume curve for the left ventricle. The upper dashed line is the total pressure that would be attained during an isovolumic contraction. The developed pressure is the difference between

the total pressure and the end-diastolic pressure. At a small end-diastolic volume (A) the contraction is isovolumic and only pressure is attained (B). At a larger end-diastolic volume (C) the left ventricle has the potential to attain a higher pressure (E). However, if the ventricle is only allowed to attain the same total pressure as during the previous systole then the ventricle will eject volume from B to D. At an even higher end-diastolic volume (F) an even greater stroke volume will be ejected if the ventricle is again only allowed to attain the same total pressure as the two previously described contractions. This type of analysis clearly illustrates the effect of varying end-diastolic volume (preload) or the Frank-Starling mechanism on left ventricular mechanics.

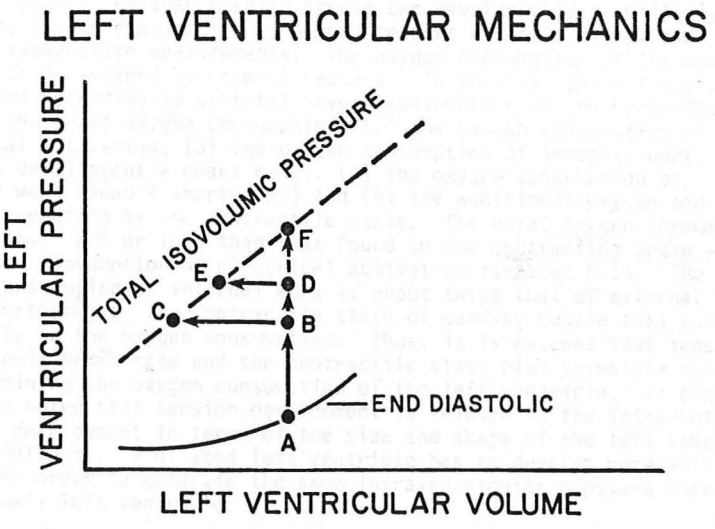
Figure 6



A similar type of analysis can be made for a change in the contractile state and this is shown in Fig. 6. The bottom solid curve is the diastolic pressure-volume curve. The lower dashed line is the total pressure that would be attained during an isovolumic contraction under control conditions, and the upper dashed line is the total pressure that would be attained during an isovolumic contraction at an increased contractile state. At the control contractile state and a given end-

diastolic volume (A) the left ventricle has the potential to attain a certain pressure (E) during an isovolumic contraction. However, if the ventricle is only allowed to attain a lower pressure (B), the ventricle will eject a stroke volume (B to C). At an increased contractile state and the same end-diastolic volume (A) the left ventricle has the potential to attain a higher pressure (F) during an isovolumic contraction. Again, however, if the ventricle is only allowed to attain the same lower pressure (B), then the ventricle will eject a larger stroke volume (B to D). This type of analysis illustrates the effect of an increase in the contractile state on left ventricular mechanics.

Figure 7



Finally, this same approach can be used to analyze the effect of a change in afterload and this is shown in Fig. 7. At a given end-diastolic volume (A) the left ventricle has the potential to attain a certain pressure (F) during an isovolumic contraction. If the ventricle is required to attain a pressure (D) it will eject a stroke volume (D to E). However, if the ventricle is only required to attain a lower pressure (B) it will eject a larger stroke volume (B to C). Thus, if the left ventricle is required to develop less pressure, it will eject a larger stroke volume. This type of analysis illustrates the effect of afterload on left ventricular mechanics. It is an understanding of this response that led to the use of afterload reduction therapy in the treatment of heart disease.

C. Myocardial Energetics

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18. Sonnenblick EH, Ross J Jr, Braunwald E: Oxygen consumption of the heart: Newer concepts of its multifactoral determination. Am J Cardiol 22:328, 1968.

19. Braunwald E: The determinants of myocardial oxygen consumption. Physiologist 12:65, 1969.

The determinants of myocardial energy use have been investigated for many years. Because cardiac muscle can develop only a small oxygen debt, its oxygen consumption is a good measure of total energy use during steady-state measurements. The oxygen consumption of the myocardium is determined by several factors. In general, the currently recognized determinants of total oxygen consumption of the myocardium are (1) the basal oxygen consumption, (2) the oxygen consumption of electrical activation, (3) the oxygen consumption of internal work (tension development X heart rate), (4) the oxygen consumption of external work (load X shortening) and (5) the additional oxygen consumption required by the contractile state. The basal oxygen consumption is low - 20% or less than that found in the contracting organ - and the oxygen consumption of electrical activation is about 0.5%. The oxygen consumption of internal work is about twice that of external work. Furthermore, the contractile state of cardiac muscle adds substantially to the oxygen consumption. Thus, it is evident that tension development, heart rate and the contractile state play principle roles in determining the oxygen consumption of the left ventricle. It especially should be noted that tension development is related to the intraventricular pressure development in terms of the size and shape of the left ventricle (Laplace effect). A dilated left ventricle has to develop more wall tension in order to generate the same intraventricular pressure than does a small left ventricle.

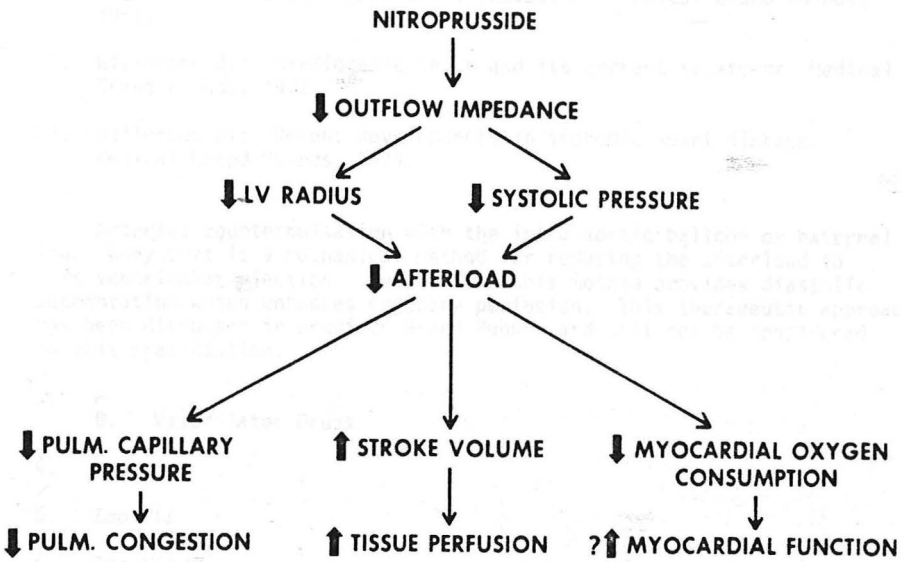
In clinical studies the tension-time index (area under left ventricular or aortic pressure curve during systole X heart rate) and the double product (peak systolic pressure X heart rate) have been used as indicators of myocardial oxygen demand. These estimates are in error if the size and shape of the left ventricle are altered.

D. Concept of Afterload Reduction Therapy in Heart Disease

5. *Loc Cit*

20. Guiha NH, Cohn JN, Mikulic E, Franciosa JA, Limas CJ: Treatment of refractory heart failure with infusion of nitroprusside. New Eng J Med 291:587, 1974.

Figure 8



The concept of the beneficial effects of afterload reduction in left ventricular failure as proposed by Cohn is shown in Fig. 8. The relaxation effect of nitroprusside on the smooth muscle of the systemic resistance vessels causes a decrease in outflow impedance. The increased emptying of the left ventricle causes a decrease in LV radius which, along with the decrease in systolic pressure development, causes a decrease in wall tension development or afterload. This should then provide an effective mechanism for (1) reducing pulmonary congestion by reducing left ventricular filling pressure, (2) increasing tissue perfusion by increasing stroke volume and cardiac output and (3) reducing myocardial oxygen consumption which may increase left ventricular function. This design by Cohn does not consider the relaxation effect of nitroprusside on the smooth muscle of the systemic capacitance vessels which also plays a role in reducing pulmonary congestion.

II. Clinical Methods of Afterload Reduction

A. Arterial Counterpulsation

21. Mitchell JH: Acute coronary occlusion: hemodynamic alterations and possible role of assisted circulation. Medical Grand Rounds, 1965.

22. Willerson JT: Cardiogenic shock and its current treatment. Medical Grand Rounds, 1972.

23. Willerson JT: Recent developments in ischemic heart disease. Medical Grand Rounds, 1974.

Arterial counterpulsation with the intra-aortic balloon or external lower body suit is a mechanical method for reducing the afterload to left ventricular ejection. In addition this method provides diastolic augmentation which enhances coronary perfusion. This therapeutic approach has been discussed in previous Grand Rounds and will not be considered in this presentation.

B. Vasodilator Drugs

4. *Loc Cit*

5. *Loc Cit*

6. *Loc Cit*

24. Chidsey CA III, Gottlieb TB: The pharmacologic basis of antihypertensive therapy: the role of vasodilator drugs. Prog Cardiovas Dis 17:99, 1974.

25. Sharpey-Schafer EP, Ginsburg J: Humoral agents and venous tone. Effects of catecholamines, 5-hydroxytryptamine, histamine, and nitrates. Lancet 2:1337, 1962.

26. Schlant RC, Tsagaris TS, Robertson RJ: Studies on the acute cardiovascular effects of intravenous sodium nitroprusside. Am J Cardiol 9:51, 1962.

27. Mason DT, Braunwald E: The effects of nitroglycerin and amyl nitrate on arteriolar and venous tone in the human forearm. Circulation 32:755, 1965.

28. Abboud RM, Schmidt PG, Eckstein JW: Vascular responses after alpha adrenergic receptor blockade. I. Responses of capacitance and resistance vessels to norepinephrine in man. J Clin Invest 47:1, 1968.

29. Miller RR, Vismara LA, Williams DO, Amsterdam EA, Mason DT: Pharmacological mechanisms for left ventricular unloading in clinical congestive heart failure. Differential effects of nitroprusside, phentolamine, and nitroglycerin on cardiac function and peripheral circulation. Circ Res 39:127, 1976.

30. Freis ED, Rose JC, Higgins TF, Finnerty FA Jr, Kelley RT, Partenope EA: The hemodynamic effects of hypotensive changes in man IV. 1-hydrazinophthalazine. Circulation 8:199, 1953.

31. Stunkard A, Wertheimer L, Redisch, W: Studies on hydralazine; evidence for a peripheral site of action. J Clin Invest 33: 1047, 1954.

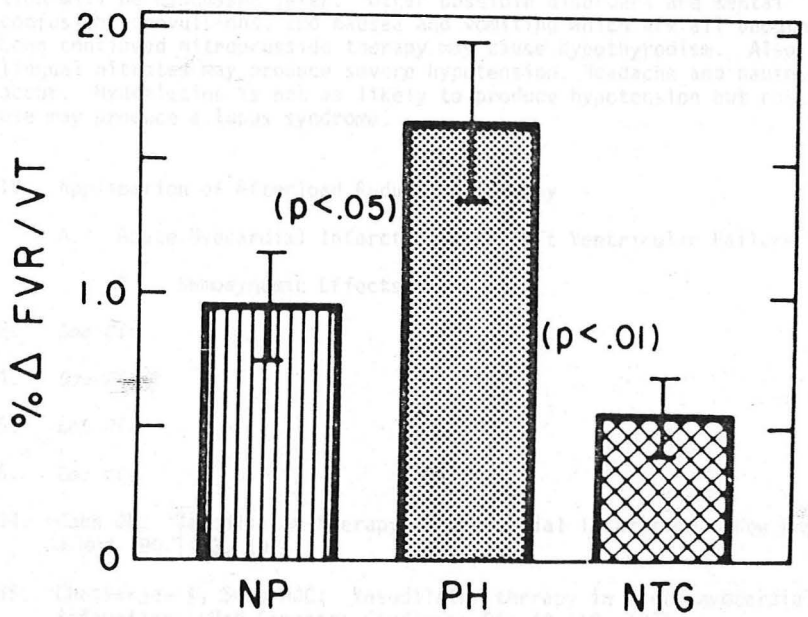
32. Åblad A, Johnsson G: Comparative effects of intra-arterially administered hydralazine and sodium nitrate on blood flow and volume of forearm. Acta Pharmacol et Toxicol 20:1, 1963.

33. Åblad B: A study of the mechanism of the hemodynamic effects of hydralazine in man. Acta Pharmacol Toxicol 20(suppl I):1, 1963.

1. Effect on Systemic Resistance and Capacitance Vessels

Vasodilator drugs have a relaxing action on the vascular smooth muscle of the systemic resistance and capacitance vessels. However, there is a differential effect of this group of drugs on these two vascular beds.

Figure 9



The different effects of some of these agents was studied by Miller *et al* and the important part of their results is shown in Fig. 9. They studied the relation of percent change in forearm vascular resistance (FVR) to percent change in forearm venous tone (VT) after the administration of sodium nitroprusside (NP), phentolamine (PH) and nitoglycerin (NTG). A FVR/VT ratio of 1.0 indicates a relatively equal degree of relaxation of systemic resistance and systemic capacitance vessels. Nitroprusside produced a balanced dilation of the systemic resistance and capacitance vascular beds. Phentolamine caused a greater systemic arteriovascular dilation and nitroglycerin resulted in a predominant systemic venous relaxation.

Hydralazine (apresoline) is another vasodilator drug that has been used for afterload reduction therapy. The vasodilator action of this agent is confined almost exclusively to the systemic resistance vessels and it causes a relatively pure reduction in arterial impedance.

2. Possible Complications of Vasodilator Therapy

The most important and serious complication of intravenous vasodilation therapy is sudden unexpected hypotension. This is particularly a problem in patients with acute myocardial infarctions and pump failure. The effect of this type of therapy on the size of the myocardial infarction will be discussed later. Other possible disorders are mental confusion, convulsions, and nausea and vomiting which are all uncommon. Long continued nitroprusside therapy may cause hypothyrodism. Also sublingual nitrates may produce severe hypotension. Headache and nausea may occur. Hydralazine is not as likely to produce hypotension but continued use may produce a lupus syndrome.

IV. Application of Afterload Reduction Therapy

A. Acute Myocardial Infarction with Left Ventricular Failure

1. Hemodynamic Effects

2. *Loc Cit*

4. *Loc Cit*

5. *Loc Cit*

6. *Loc Cit*

34. Cohn JN: Vasodilator therapy of myocardial infarction. New Eng J Med 290:1433, 1974.

35. Chatterjee K, Swan HJC: Vasodilator therapy in acute myocardial infarction. Mod Concepts Cardiovas Dis 43:119, 1974.

36. Hamosh P, Cohn JN: Left ventricular function in acute myocardial infarction. J Clin Invest 50:523, 1971.

37. Franciosa JA, Limas CJ, Guiha NH, Rodriguera E, Cohn JN: Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. Lancet 1:650, 1972.

38. Chatterjee K, Parmley WW, Ganz W, Forrester J, Walinsky P, Crexells C, Swan HJC: Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. Circulation 48:1183, 1973.

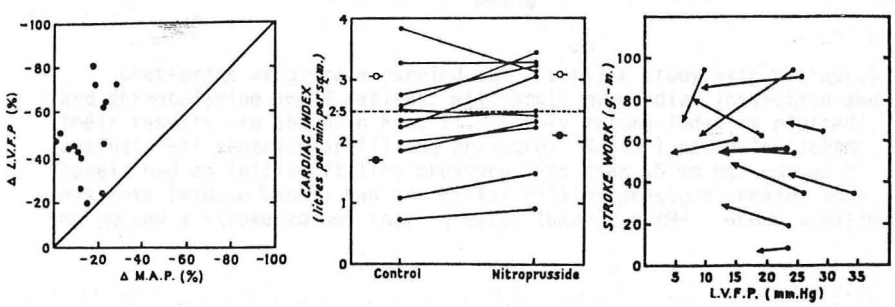
39. Chatterjee K, Swan HJC, Kaushik VS, Jobin G, Magnusson P, Forrester JS: Effects of vasodilator therapy for severe pump failure in acute myocardial infarction on short-term and late prognosis. Circulation 53:797, 1976.

40. Mantle JA, Russell RO Jr, Moraski RE, Rackley CE: Isosorbide dinitrate for the relief of severe heart failure after myocardial infarction. Am J Cardiol 37:263, 1976.

In patients with an acute myocardial infarction there tends to be an increase in left ventricular end-diastolic pressure and a decrease in cardiac output. If the left ventricle end-diastolic pressure becomes too high, then the pulmonary capillary pressure increases to excessively high levels and pulmonary congestion and edema occur. If the cardiac output becomes too low, then cardiac shock ensues with inadequate perfusion to vital areas. In this situation it is important to reduce filling pressure and to increase cardiac output.

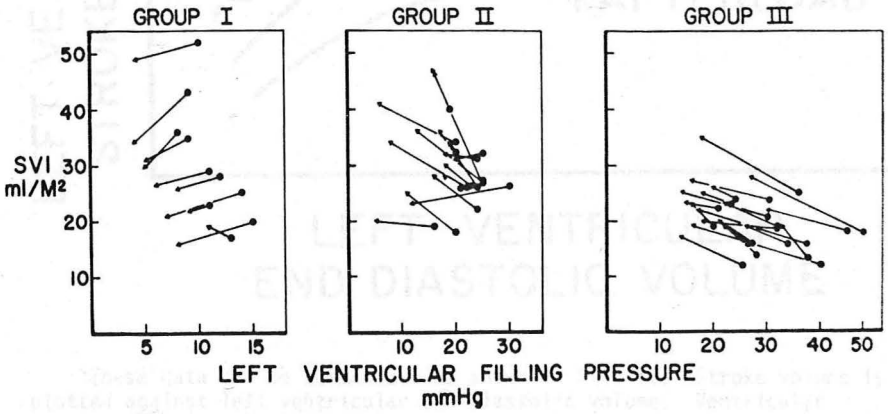
Traditionally the approach to this clinical situation has been to treat the low cardiac output with inotropic agents and the pulmonary congestion by reducing filling pressure. Reducing left ventricular filling pressure relieves the pulmonary congestion and its symptoms, but cardiac output may decrease further. Inotropic agents have not been found to be of great benefit in increasing the cardiac output and, in addition, tend to increase myocardial oxygen demands.

Figure 10



More recently several groups of investigators have successfully treated the elevated left ventricle filling pressure and low cardiac output with afterload reduction therapy. Cohn and his coworkers have studied the effects of sodium nitroprusside infusion in 15 patients with acute myocardial infarction and their results are shown in Fig. 10. In the left panel the change in left ventricular filling pressure [ΔLVFP(%)] is plotted against the change in mean arterial pressure [ΔMAP(%)]. There was a much more marked drop in left ventricular filling pressure (average 50%) than in mean arterial pressure (average 16%). In the middle panel is shown the cardiac index before and during the nitroprusside infusion. There was little change in the cardiac index in patients with a control value above 2.5 l/min/sq m (open circles), but there tended to be an increase in the patients with a control value below 2.5 l/min/ sq m (closed circles). In the right panel stroke work is plotted against left ventricular filling pressure. Each patient is represented by a line connecting a black circle (control) to an arrowhead (nitroprusside). The heavy line is the average for the group. Left ventricular filling pressure fell from an average value of 23 to 11 mm Hg and stroke work remained essentially constant. This may indicate an improvement in left ventricular function.

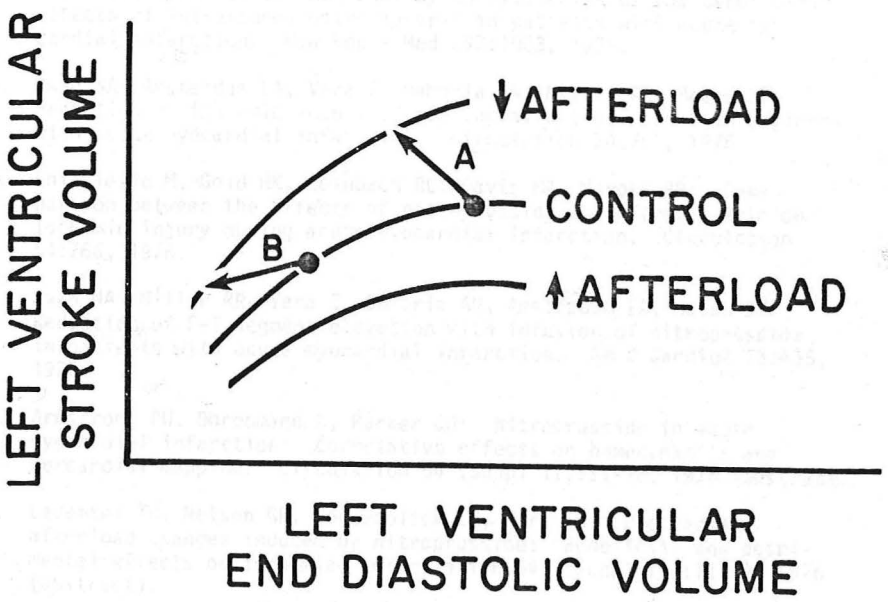
Figure 11



Chatterjee *et al* have carried out a similar study with nitroprusside and phenotolamine in 38 patients with acute myocardial infarction and their results are shown in Fig. 11. Stroke volume index is plotted against left ventricular filling pressure. Group 1 patients (left panel) had an initial filling pressure less than 15 mm Hg. Group 2 patients (middle panel) had an initial filling pressure greater than 15 mm Hg and a stroke volume index greater than 20 ml/M^2. Group 3 patients

(right panel) had a filling pressure greater than 15 mm Hg and a stroke volume index less than 20 ml/M^2. In all three groups the usual hemodynamic response was aecrease in systemic vascular resistance and a slight decrease in mean arterial pressure. A concomitant increase in stroke volume index with a decrease in left ventricular filling pressure was observed consistently only in Group II and Group III patients. Even the sickest patients (Group III) had a 20 to 30% increase in stroke volume index with about a 35% decrease in left ventricular filling pressure. In Group I patients the fall in left ventricular filling pressure was usually accompanied by a fall in stroke volume index.

Figure 12



These data can be summarized as shown in Fig. 12. Stroke volume is plotted against left ventricular end-diastolic volume. Ventricular function curves are shown for control conditions and during decreased and increased afterload. At a high filling pressure (20 mm Hg) with afterload reduction there is a drop in filling pressure to 15 mm Hg (line A) with an increase in stroke volume. At a low filling pressure (10 mm Hg) with a similar afterload reduction there is a similar 5 mm Hg drop in filling pressure (line B) with a decrease in stroke volume. This clearly demonstrates the importance of giving afterload reduction therapy only to patients with high left ventricular filling pressures.

2. Effect on the Size of a Myocardial Infarction

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44. Awan NA, Amsterdam EA, Vera Z, DeMaria AN, Miller RR, Mason DT: Reduction of ishcemic injury of sublingual nitroglycerin in patients with acute myocardial infarction. Circulation 54:761, 1976.

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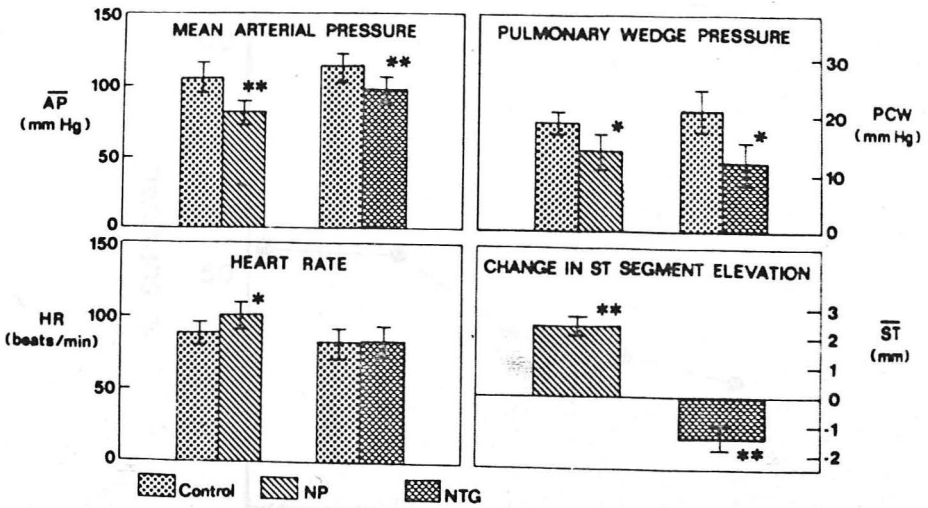
There has been much emphasis recently on therapeutic means to reduce the size of a myocardial infarction. However, one of the major problems in this area has been the development of a reliable method to quantitate the amount of irreversibly damaged cardiac muscle. The method that has been most widely used is S-T segment mapping and it has many limitations.

Figure 13



Several investigators have utilized S-T segment mapping in both patients and animals to study the effect of afterload reduction therapy on infarction size with highly conflicting results. An example of the type of studies that have been done is shown in Fig. 13. Five patients with acute myocardial infarction received nitroglycerin and nitroprusside in doses that caused the same reduction in mean arterial pressure. This caused a similar reduction in pulmonary wedge pressure but heart rate increased only after nitroprusside. Further nitroprusside caused an increase in mean S-T segment elevation and nitroglycerin caused a decrease in this measurement.

These same investigators found similar results in dogs after experimental myocardial infarction. Other groups have found the opposite effects in both patients and experimental animals.

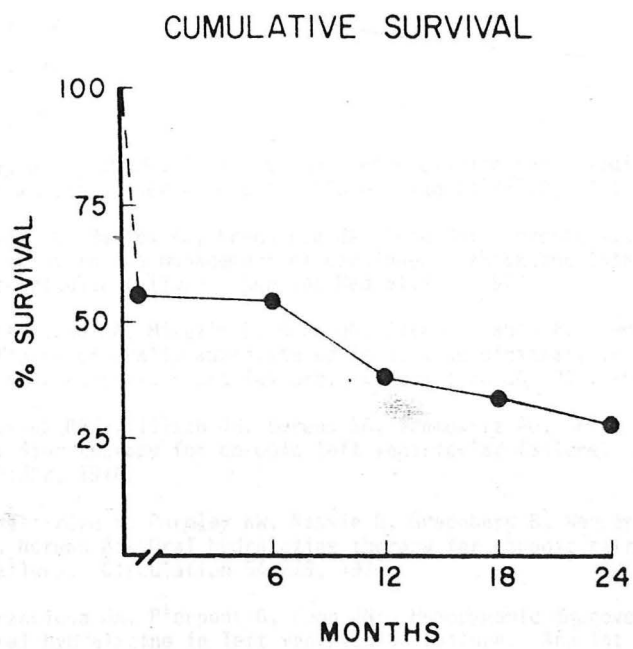
The question of whether or not various vasodilator drugs affect the size of a myocardial infarction cannot be definitely answered from the experimental evidence available at this time. Much work is currently being done in this area and it is urgently needed to solve this dilemma.

3. Long-term prognosis

4. *Loc Cit*

39. *Loc Cit*

Figure 14



The studies with afterload reduction therapy in acute myocardial infarction have clearly demonstrated beneficial short term hemodynamic effects. However, the effect of this therapy on the size of a myocardial infarction is highly controversial. Regardless of the results of these acute findings, the long term prognosis for patients receiving afterload reduction therapy remains unfavorable. This has also been documented by Chatterjee *et al* and is shown in Fig. 14. Forty-three patients with severe pump failure complicating acute myocardial infarction were treated with afterload reduction. Twenty-four of these patients (56%) survived and were discharged from the hospital. Of these 24 patients, 14 died 1 to 25 months (average 9.2 months) after discharge usually of pump failure. The ten surviving patients have been followed for 15 to 32 months (average 24 months) and the cummulative survival at 24 months was 28%. Thus, the long term prognosis of patients with pump failure accompanying acute myocardial infarction is poor even though they can be brought through their acute phase with afterload reduction therapy. This is not surprising since patients with pump failure probably have a large percentage of their left ventricular mass irreversibly damaged.

B. Refractory Chronic Left Ventricular Failure

4. *Loc Cit*

5. *Loc Cit*

6. *Loc Cit*

50. Majid PA, Sharma B, Taylor SH: Phentolamine for vasodilator treatment of severe heart failure. Lancet 2:719, 1971.

51. Cohn JN, Mathew KJ, Franciosa JA, Snow JA: Chronic vasodilator therapy in the management of cardiogenic shock and intractable left ventricular failure. Ann Int Med 81:777, 1974.

52. Franciosa JA, Mikulic E, Cohn JN, Jose E, Fabie A: Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure. Circulation 50:1020, 1974.

53. Kovick RB, Tillisch JH, Berens SC, Bramowitz AD, Shine KI: Vasodilator therapy for chronic left ventricular failure. Circulation 53:322, 1976.

54. Chatterjee K, Parmley WW, Massie B, Greenberg B, Werner J, Klausner S, Norman A: Oral hydralazine therapy for chronic refractory heart failure. Circulation 54:879, 1976.

55. Franciosa JA, Pierpont G, Cohn JN: Hemodynamic improvement after oral hydralazine in left ventricular failure. Ann Int Med 86: 388, 1977.

56. Williams DO, Bommer WJ, Miller RR, Amsterdam EA, Mason DT: Hemodynamic assessment of oral peripheral vasodilator therapy in chronic congestive heart failure: prolonged effectiveness of isosorbide dinitrate. Amer J Cardiol 39:84, 1977.

57. Pierpont G, Franciosa JA, Cohn JN: Equivalent hemodynamic effects of nitroprusside and hydralazine-nitrate combination in left ventricular failure. Circuation 54 (Suppl II):II-215, 1976 (abstract).

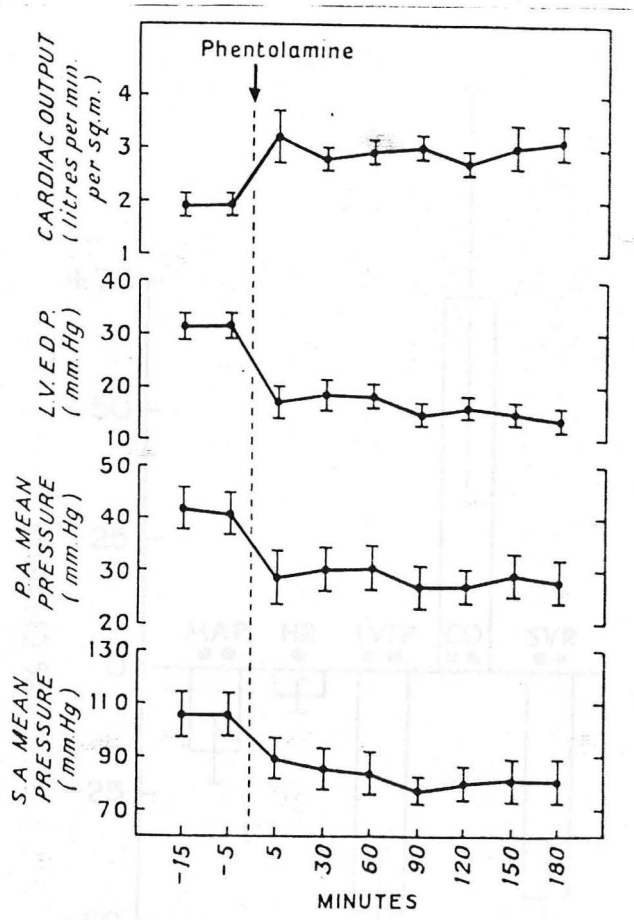
58. Massie B, Werner J, Greenberg B, Chatterjee K, Parmley WW: Hemodynamic effects of combined oral hydralazine and nonparenteral nitrates in severe heart failure. Am J Cardiol 39:298, 1977 (abstract).

59. Schreiber R, Loeb H, Gunnar R: Hemodynamic benefit following oral phentolamine in patients with chronic cardiac failure. Am J Cardiol 39:297, 1977 (abstract).

Chronic congestive heart failure which is refractory to conventional therapy with digitalis and diuretics is commonly seen in patients

with advanced cardiomyopathies and severe ischemic heart disease. In these patients with marked chronic pump failure, there occurs a reflex increase in systemic vascular resistance so that arterial pressure is maintained. This vasoconstriction is predominantly mediated through the sympathetic adrenergic receptors in the systemic resistance vessels. In a sense this homeostatic mechanism is counter-productive since it increases pressure work of the failing, dilated left ventricle. It thus appeared possible that lowering systemic vascular resistance would cause beneficial hemodynamic effects for the patient.

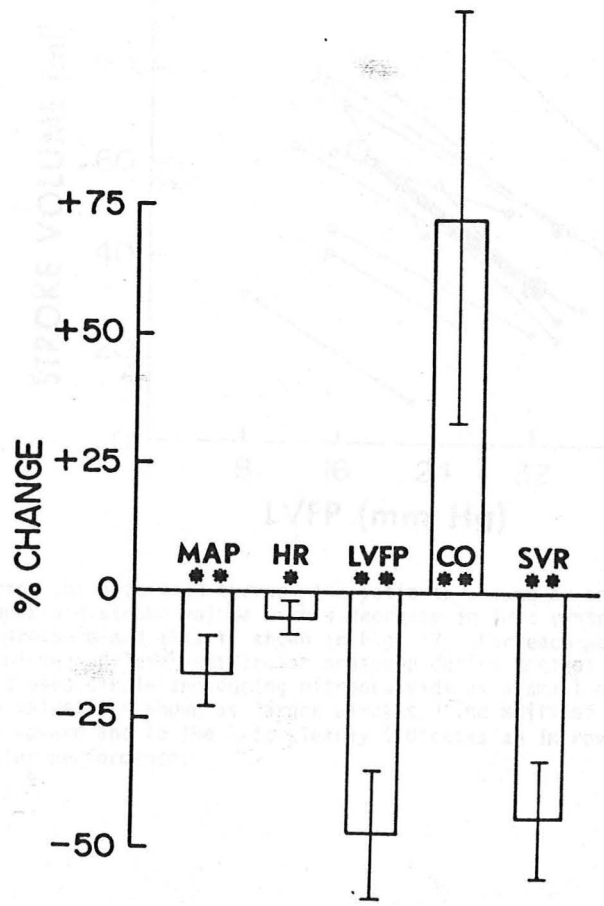
Figure 15



Taylor and his group in Leeds, England were one of the first to attempt this form of treatment for refractory left ventricular failure and their results are shown in Fig. 15. Phentolamine was infused into 6 patients at a rate that reduced the mean systemic arterial pressure (S.A. Mean Pressure) by 25 mm Hg for 3 hours. There was a sustained increase in cardiac output and a fall in left ventricular end-diastolic pressure (LVEDP) and mean pulmonary arterial pressure (PA Mean Pressure). In addition, chest radiographs before and after the infusion showed a reduction in pulmonary congestion and in heart size.

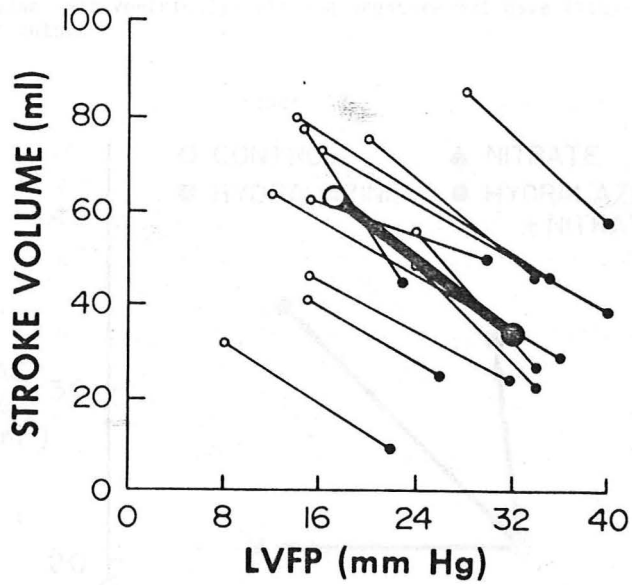
Cohn and his group infused sodium nitroprusside into 18 patients with refractory heart failure and their results are shown in Figs. 16 and 17. Fourteen of the 18 patients stated that they were less short of breath. Also sweating and arrythmias tended to disappear.

Figure 16



In Fig. 16 the % change that occurred in mean arterial pressure (MAP), heart rate (HR), left ventricular filling pressure (LVFP), cardiac output (CO) and systemic vascular resistance (SVR) during the infusion are demonstrated. Mean arterial pressure fell from 99 to 83 mm Hg (-16%), heart rate decreased from 96 to 91 (beats/min) (-5%), left ventricular filling pressure fell from 32 to 17 mm Hg (-47%), cardiac output increased from 2.98 to 5.20 l/min (+74%), and systemic vascular resistance decreased from 27 to 13 resistance units (-52%). In 13 patients the infusion was contained for 1 to 2 hours with maintained improvement and in 5 patients the infusion was continued for 72 hours.

Figure 17

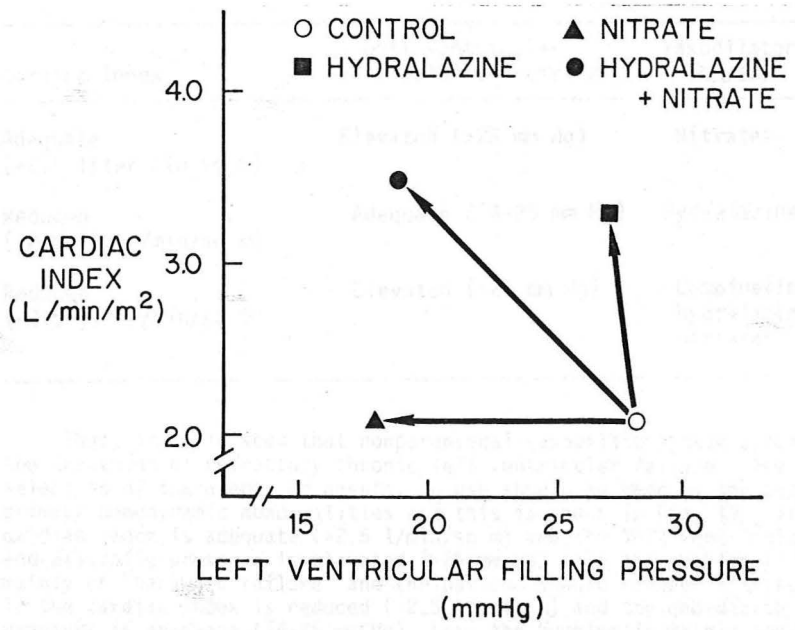


During the afterload therapy the patients showed an increase in stroke work and stroke volume with a decrease in left ventricular filling pressure and this is shown in Fig. 17. For each patient the stroke volume and left ventricular pressure during control is plotted as a small closed circle and during nitroprusside as a small open circle. The mean values are shown as larger circles. The shift of this relationship upward and to the left clearly indicates an improvement in left ventricular performance.

Cohn and his group were also able to treat a patient with cardiogenic shock and refractory failure due to coronary disease with a 21 day infusion of sodium nitropruside followed by chronic administration of nitrates by mouth and topically for 8 months. Hemodynamic and clinical improvement were maintained during this time.

However, it still remained to be shown that afterload reduction could be used for the long-term therapy of patients with chronic refractory left ventricular failure. Several groups have now treated this condition using a sublingual or oral nitrate for reduction in preload and phenoxybenzamine or hydralazine for reduction in afterload. In patients with refractory chronic left ventricular failure, Chatterjee, Parmley and their group and Cohn and his group have demonstrated that hydralazine will increase cardiac output but has little effect on left ventricular filling pressure. It has also been shown that the nitrates will decrease left ventricular filling pressure but have little effect on cardiac output.

Figure 18



A study by Chatterjee and Parmley which illustrates this point is shown in Fig. 18. The patients were given 50 to 75 mg hydralazine

every 6 hours and oral or sublingual isosorbide-dinitrate, either alone or in combination. Cardiac index is plotted against left ventricular filling pressure. During the control study (open circle) the filling pressure was 28 mm Hg and the cardiac index was 2.1 l/min/m^2. The administration of a nonparenteral nitrate (triangle) caused a decrease in left ventricular filling pressure to 18 mm Hg with no change in the cardiac index (Where is the descending limb!). Hydralazine (square) caused an increase in the cardiac index to 3.3 l/min/m^2 but little change in filling pressure. With the combination of a nitrate and hydralazine (closed circle) the cardiac index increased to 3.5 l/min/m^2 and the fillling pressure decreased to 19 mm Hg.

Figure 19

Use of Hemodynamic Measurements in Selecting Vasodilator Therapy for Chronic Heart Failure

Cardiac Index	Left Ventricular End Diastolic Pressure	Vasodilator Therapy
Adequate (>2.5 liter/min sq m)	Elevated (>25 mm Hg)	Nitrates
Reduced (<2.5 liter/min/sq m)	Adequate (14-25 mm Hg)	Hydralazine
Reduced (<2.5 liter/min/sq m)	Elevated (>25 mm Hg)	Combination of hydralazine and nitrates

Thus, it would seem that nonparenteral vasodilators have a role in the treatment of refractory chronic left ventricular failure. The selection of the agent, or agents, to use should be made on the basis of primary hemodynamic abnormalities and this is shown in Fig. 19. If the cardiac index is adequate (>2.5 l/min/sq m) and the left ventricular end-diastolic pressure is elevated (>25 mm Hg) then the problem is mainly of "backward failure" and the patient should receive nitrates. If the cardiac index is reduced (<2.5 l/m/sq m) and the end-diastolic pressure is adequate (14-25 mm Hg), then the problem is mainly one of "forward failure" and the patient should receive hydralazine. If the cardiac index is reduced and the end-diastolic pressure is elevated, then the problem is one of both "backward and forward failure" and the

patient should receive both oral nitrates and hydralazine. Even though the number of patients that have been studied is small and the duration of follow-up is relatively short, it would appear that afterload reduction therapy may play an important role in the therapy of refractory chronic left ventricular failure. However, before a final appraisal can be made, more studies are needed and these are currently being carried out in many centers.

C. Valvular Disease

1. Mitral Regurgitation

4. *Loc Cit*

5. *Loc Cit*

60. Wiggers CJ, Feil H: The cardio-dynamics of mitral insufficiency. Heart 9:149, 1922.

61. Welch GH, Braunwald E, Sarnoff SJ: Hemodynamic effects of quantitatively varied experimental mitral regurgitation. Circ Res 5:546, 1957.

62. Chatterjee K. Parmley WW, Swan HJC, Berman G, Forrester J, Marcus HS: Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvar apparatus. Circulation 48:684, 1973.

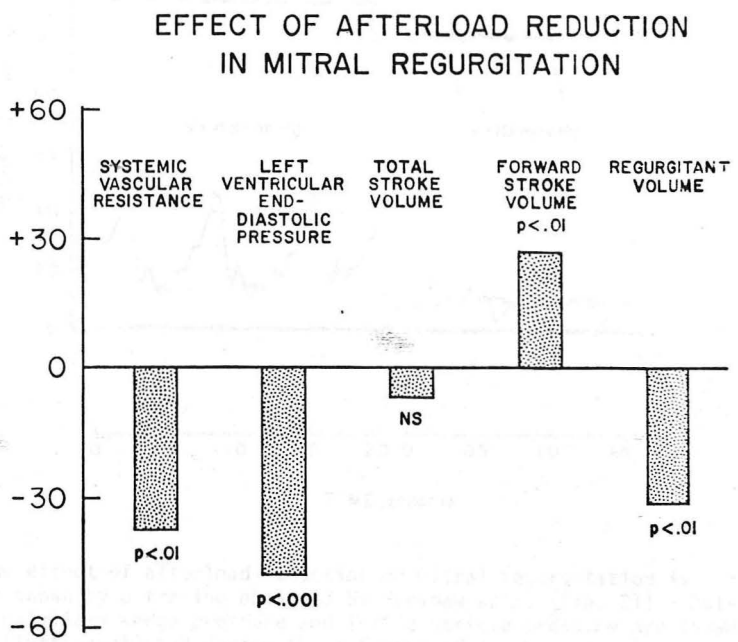
63. Goodman DJ, Rossen RM, Holloway EL, Alderman EL, Harrison DC: Effect of nitroprusside on left ventricular dynamics in mitral regurgitation. Circulation 50:1025, 1974.

64. Sniderman AD, Marpole DGF, Palmer WH, Fallen EL: Response of the left ventricle to nitroglycerin in patients with and without mitral regurgitation. Br H Jour 36:357, 1974.

65. Harshaw CW, Grossman W, Munro AB, McLaurin LP: Reduced systemic vascular resistance as therapy for severe mitral regurgitation of valvular origin. Ann Int Med 83:312, 1975.

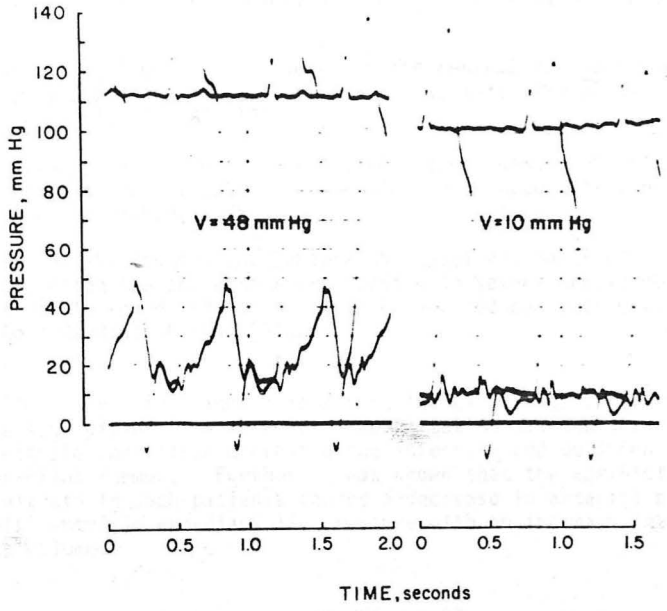
It has been shown that reducing the resistance to ejection or aortic impedance in experimentally produced mitral regurgitation will increase forward cardiac output and reduce backward flow. Because of this experimental finding, afterload reduction has been used to treat mitral regurgitation due both to valvular origin and to papillary muscle dysfunction.

Figure 20



An example of such a therapeutic approach for the treatment of mitral regurgitation of valvular origin by Goodman *et al* is shown in Fig. 20. Sodium nitroprusside was infused intravenously resulting in a decrease in systemic vascular resistance from 26 to 16 resistance units (-37%), a decrease in left ventricular end-diastolic pressure from 17 to 9 mm Hg (-47%), no change in total stroke volume, an increase in forward stroke volume from 45 to 57 ml (+27%) and a decrease in regurgitation volume from 62 ml to 43 ml (-31%).

Figure 21



The effect of afterload reduction on mitral regurgitation is further shown by a tracing obtained by Harshaw *et al* (Fig. 21). Pulmonary capillary wedge pressure and left ventricle pressure are shown before (left panel) and during the infusion of sodium nitroprusside (right panel). The V wave in the pulmonary capillary wedge pressure is essentially abolished along with a significant reduction in mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure.

It seems to have been clearly established that beneficial hemodynamic effects can be attained acutely by the intravenous administration of afterload reducing agents. Such therapy may allow delay of surgery in seriously ill patients with either acute and/or chronic severe mitral regurgitation until they are stabilized and are safer surgical candidates. Further, it will be of interest to see if the long-acting non-parenteral agents will have any value in the chronic treatment of patients with mitral regurgitation.

2. Aortic Regurgitation

4. *Loc Cit*

5. *Loc Cit*

66. Hurst JH (Ed): The Heart, edition 3, New York, McGraw-Hill, 1974, p. 930.

67. Delius W, Enghoff E: Studies of the central and peripheral hemodynamic effects of amyl nitrate in patients with aortic insufficiency. Circulation 42:787, 1970.

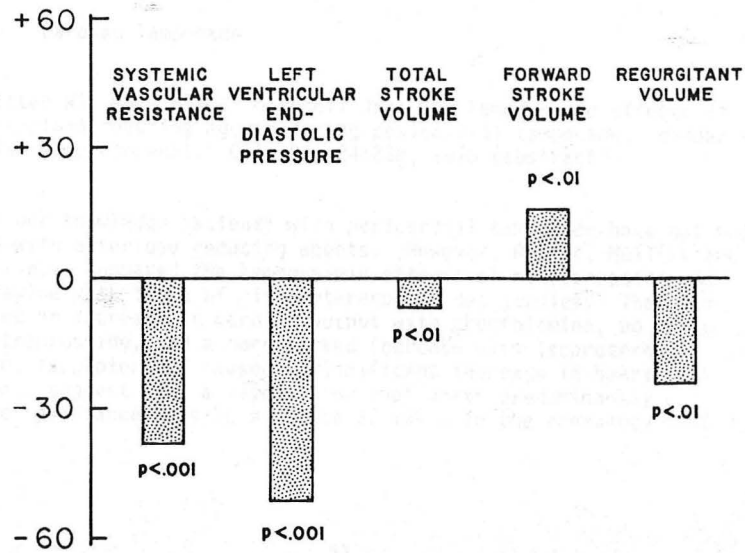
68. Bolen JL, Alderman EL: Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. Circulation 53:879, 1976.

69. Miller RR, Vismara LA, DeMaria AN, Salel AF, Mason DT: Afterload reduction therapy with nitroprusside in severe aortic regurgitation: improved cardiac performance and reduced regurgitant volume. Am J Cardiol 38:564, 1976.

One of the first indications that the use of vasodilators might reduce regurgitant flow in aortic regurgitation was the observation that amyl nitrate inhalation decreased the intensity and duration of the Austin-Flint murmur. Further it was shown that the administration of amyl nitrate in such patients caused a decrease in arterial pressure and in left ventricle end-diastolic pressure with an increase in forward stroke volume.

Figure 22

EFFECT OF AFTERLOAD REDUCTION IN AORTIC REGURGITATION



Several groups of investigators have used afterload reduction in the acute treatment of aortic regurgitation. An example of such a therapeutic approach by Miller *et al* is shown in Fig. 22. Sodium nitroprusside was infused intravenously resulting in a decrease in systemic vascular resistance from 18 to 11 resistance units (-39%), a decrease in left ventricle end-diastolic pressure from 23 to 11 mm Hg (-52%), a small decrease in total stroke volume (-8%), an increase in forward stroke volume from 54 to 62 ml (+15%) and a decrease in regurgitated volume from 72 to 54 ml (-25%).

Chatterjee and Parmley have treated a case of acute severe aortic insufficiency due to bacterial endocarditis with sublingual isosorbide dinitrate. The administration of increasing doses (2.5, 5, and 10 mg) caused little change in heart rate (HR), no fall in mean arterial pressure (MAP), an increase in cardiac output (CO), a decrease in systemic vascular resistance (SVR), a decrease in pulmonary capillary wedge pressure (PCW), and an increase in forward stroke volume (FSV). The patient was maintained on this regime until she was stabilized and able to go to surgery for valve replacement.

In cases of acute aortic insufficiency the benefical hemodynamic effects of afterload reduction therapy may be critical in maintaining a patient until more definite surgical therapy can be performed. In cases of chronic aortic insufficiency when compensation is no longer possible with conventional forms of therapy (digitalis and diuretics) and when surgical therapy is contraindicated or needs to be deferred, the addition of afterload reduction therapy may produce clinical improvement. By reducing the size of the left ventricle, its function may be preserved for a longer period of time. The long term effects of such therapy may be of benefit and need to be investigated.

D. Cardiac Tamponade

70. Ritter WS, Mullins CB, Mitchell JH: The hemodynamic effects of afterload reducing agents during pericardial tamponade: comparison with isoproterenol. Clin Res 24:238, 1976 (abstract).

To our knowledge patients with pericardial tamponade have not been treated with afterload reducing agents. However, Ritter, Mullins and Mitchell have compared the hemodynamic effects of nitroprusside and phentolamine with those of isoproterenol in dog studies. They demonstrated an increase in cardiac output with phentolamine, no change with nitroprusside, and a more marked increase with isoproterenol. In addition, isoproterenol caused a significant increase in heart rate. These data suggest that a vasodilator that works predominantly on systemic resistance vessels might be of value in the emergency medical

treatment of cardiac tamponade prior to pericardial drainage. Agents that predominantly dilate the systemic capacitance vessels would be contraindicated because a high filling pressure is needed.

V. Conclusions

The use of afterload reduction therapy in the treatment of heart disease is a relatively new approach which is currently receiving much interest. The traditional therapy of regulating preload or filling pressure and of attempting to increase the contractile state of the failing left ventricle is often inadequate for relieving the symptoms of "forward and backward failure". In such a clinical situation the addition of afterload reduction therapy has been of benefit by increasing cardiac output and decreasing left ventricle filling pressure. This approach has been used in acute myocardial infarction, refractory chronic failure, mitral and aortic regurgitation, and cardiac tamponade. At present this mode of therapy appears to offer the most promise in treating refractory chronic left ventricular failure. In acute myocardial infarction this approach must be used with caution until more is known about its effects on infarction size.

Further studies need to be done (1) to define precisely the role of afterload reduction therapy in the management of various types of heart disease and (2) to develop new oral vasodilator agents that are safe, reliable and longer-acting.