Afterload Reduction Therapy for Congestive Heart Failure

DEAN T. MASON, M.D.

From the Section of Cardiovascular Medicine, Departments of Medicine and Physiology, University of California, School of Medicine, Davis, California, and Sacramento Medical Center, Sacramento, California

The most important recent advance in the medical management of patients with acute and chronic congestive heart failure has been the application of systemic vasodilator drugs to reduce ventricular afterload, thereby improving low cardiac output and decreasing increased venous pressure. Although such drugs have been employed for several years to treat essential hypertension, hypertensive heart failure, acute hypertensive crises, and angina pectoris, only in the past five years has their use become widely popular in the therapy of normotensive heart failure.[1] While it can be reasoned that the vasodilator approach is a logical therapeutic extension of fundamental determinants regulating cardiac function known for many years, it is nevertheless intriguing that consideration has been delayed until the present time of such a useful concept as afterload reduction therapy in heart failure.

Regulation of Cardiac Function

The intact heart is normally governed by the intimate integration of four principal determinants regulating stroke volume and cardiac output (Fig 1): 1) preload (ventricular end-diastolic volume), 2) contractility (variable force of ventricular contraction independent of loading), 3)

afterload (ventricular systolic tension during ejection), and 4) heart rate.[2] The terms "cardiac function" and "ventricular performance" are used in the general sense to refer to the combined action of these four determinants of cardiac output, and not necessarily to the single determinant of contractility. The disturbed mechanisms operative in all types of clinical heart disease can be evaluated and accurately measured within the framework of isolated or composite disorders of these four major determinants of cardiac performance.[3] Besides affording a better understanding of the manner in which various types of heart disease lead to disturbed pump performance, appreciation of the determinants of cardiac function (Fig 1) provides the rationale for an organized approach to the integration of therapy in the management of congestive heart failure.[4]

Rationale of Afterload Reduction Therapy

Facilitation of ventricular emptying leading to increasing lowered stroke volume is the fundamental objective of therapy for heart failure. Conventional treatment of congestive heart failure has focused primarily on increasing ventricular stroke volume and cardiac output through the use of direct positive inotropic agents and concomitant diuretic therapy. In the case of patients with coronary heart disease in whom acute and chronic pump failure results principally from the impairment and loss of myocardial contractile units, an increase in the inotropic state of the remaining functioning heart muscle may insufficiently augment cardiac per-

formance. The powerful inotropic stimulus of cardiotonic agents may also increase overall myocardial oxygen demand ($M\dot{V}O_2$), which is potentially detrimental in acute ischemic heart disease. In contrast to elevating low stroke output by direct inotropic stimulation in heart failure, reducing impedance to left ventricular ejection by administration of systemic arteriolar dilator drugs provides a unique therapeutic mechanism for the augmentation of pump performance by increasing ventricular emptying, while also diminishing $M\dot{V}O_2$.[5]

Determinants of Ventricular Afterload

As with ventricular filling (preload), several factors influence afterload and impedance to left ventricular outflow. The load or tension that the left ventricle must develop to eject stroke volume constitutes ventricular afterload. Afterload is defined as the wall tension during left ventricular ejection.[5] The two principal determinants of afterload are systolic pressure and radius of the ventricle, according to the Laplace formula. In turn, systolic pressure is related to impedance to blood flow in the aorta, and the radius of the ventricular chamber is related to left ventricular volume (preload).

Determinants of Aortic Impedance

Impedance to left ventricular ejection is the instantaneous relation between the rate of change in aortic pressure and aortic flow.[5] Left ventricular outflow impedance is governed primarily by two factors: 1) the compliance (relation of pressure to flow) in the large arteries; and 2) the total peripheral vascular resistance (the rate of runoff from the systemic arterial tree) which is determined principally by the radius or cross-sectional area of the systemic arteriolar beds. Of these factors regulating impedance, systemic arteriolar resistance is the most important and the variable most subject to modification by pharmacologic vasodilation.

Determinants of Left Ventricular Energetics

In the setting of impaired ventricular performance, elevation of outflow impedance results in declines of the extent and rate of fiber shortening and reduction in the ejection fraction with the consequent elevation of left ventricular filling pressure (preload). Thus stroke volume must be maintained at increased energy costs related to the increase in intramyocardial wall tension (af-
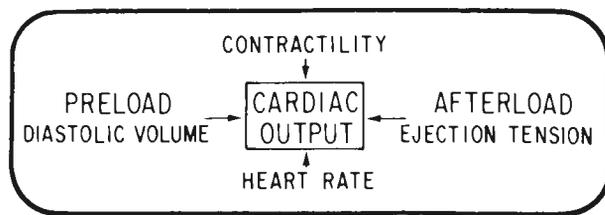

Fig 1—Representation of the four principal determinants of cardiac output.

terload) (Fig 2).[5] In severe pump failure, elevations of impedance and preload (afterload product), which are inherent consequences of the heart failure state, result in the rise of $M\dot{V}O_2$. This rise in $M\dot{V}O_2$ leads to potential myocardial ischemia and continued impairment of pump function, causing greater sympathetic-induced rise of peripheral vascular resistance with resultant increases in ventricular afterload and preload. Thus a progressively deleterious cycle adversely affecting $M\dot{V}O_2$ and pump performance is set in motion by the operation of compensatory mechanisms attempting to maintain cardiocirculatory integrity. Systemic vasodilator therapy, which produces reductions in both impedance and preload, interrupts this harmful chain of events while augmenting cardiac output, diminishing pulmonary congestion and improving myocardial energetics.[5]

Clinical Use of Systemic Vasodilators

While it has been two decades since Burch produced ganglionic blockade with the intravenous vasodilator, hexamethonium, in the relief of intractable pulmonary congestion due to left heart failure[6] and Johnson diminished acute pulmonary edema by sublingual nitroglycerin in left ventricular dysfunction,[7] the expressed purpose of those two isolated reports was clearly the reduction of increased left ventricular preload and elevated systemic venous tone in the amelioration of backward failure (pulmonary congestion) via peripheral venodilation. That vasodilators might be useful in decreasing raised peripheral arterial resistance to diminish

FIG 2—Representation of the three major determinants of myocardial oxygen consumption ($M\dot{V}O_2$). Intramyocardial systolic wall tension is left ventricular afterload which is a product of preload (left ventricular volume) and impedance (systolic blood pressure).
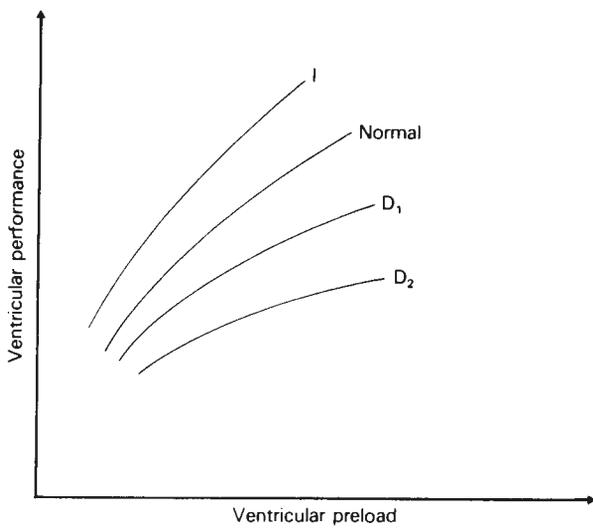
FIG 3—Ventricular function curves relating ventricular performance (cardiac output) to ventricular preload (ventricular end-diastolic pressure). Curve 1 represents increased cardiac contractility, while curves D_1 and D_2 indicate progressively severe reductions in contractility.

pump outflow impedance with improvement in forward failure (low cardiac output) was not appreciated at that time.

The pharmacologic approach of vasodilator therapy for impedance reduction was first employed clinically in normotensive severe heart failure by Majid and associates in 1971.[8] Thus, infusion of the alpha-adrenergic blocking
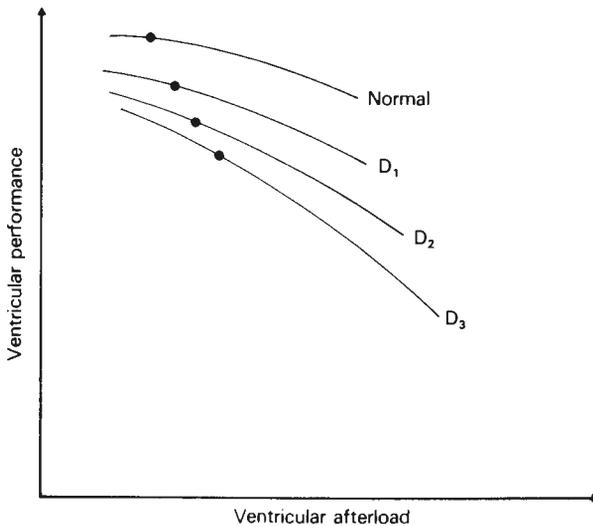

FIG 4—Ventricular function curves relating ventricular performance (cardiac output) to the aortic impedance component (total systemic vascular resistance) of ventricular afterload. This relationship becomes increasingly steep (greater depression of cardiac output) as ventricular function declines from the normal curve to the curves D_1, D_2 and D_3 indicating progressively greater depression of cardiac contractility. As cardiac dysfunction worsens, the point of ventricular function (closed circles) of the progressively failing ventricle on the spectrum of curves shifts to a higher impedance component of afterload.

agent, phentolamine, in acute myocardial infarction was observed to result in the decline of elevated systemic vascular resistance, accompanied by the rise of low cardiac output and the fall of elevated pulmonary artery pressure, without substantial alterations in systemic arterial pressure and heart rate. The modern era of afterload reduction gained momentum following reports of similar hemodynamic benefits achieved by intravenous nitroprusside in acute myocardial infarction patients.[9-11] The vasodilator concept spread rapidly and has now been extended to the management of severe chronic cardiac dysfunction of various types.[5,12,18]

As to why the idea of afterload reduction therapy of heart failure was not recognized sooner, it seems to me that this delay has been largely the result of a lack of understanding, until recently, of the critical relationships between peripheral circulatory dynamics and cardiac performance.[19] Furthermore, the relation of cardiac output to peripheral vascular activity is dependent upon left ventricular contractility. When the heart is normal, cardiac output is principally governed by systemic venous tone with the left ventricle operating on the steep ascending limb of its Frank-Starling curve (outflow-preload relation) (Fig 3); aortic impedance reduction is of little importance. In contrast, in the presence of left ventricular dysfunction, arterial resistance is elevated and cardiac output becomes strongly dependent on outflow resistance (Fig 4). Thus, the interplay between impedance (arterial resistance bed) and preload (venous capacitance bed) reductions is that preload is more important than impedance in the normal heart (cardiac output declines) (Fig 3), while in the failing heart, impedance reduction predominates over preload decline (cardiac output rises) (Fig 4).

While profound peripheral arterial and venous constriction accompanies chronic heart failure,[2] only recently has it become appreciated that the heightened adrenergic activity in response to lowered cardiac output, while seemingly useful in maintaining blood pressure, may result in a greater level of increased systemic vascular resistance than is required to sustain arterial pressure, and thus this reflex adaptive mechanism may actually further decrease cardiac output (Fig 4).[1] A harmful cycle is thereby provoked in which the heart failure patient reaches a greater depression of hemodynamics than is really optimal, systemic vascu-

lar resistance being higher and cardiac output lower than are salutary. In addition, systemic venoconstriction may also become excessive in chronic heart failure. Consequently, there occurs greater elevation of left ventricular end-diastolic pressure than is required relative to the lowered cardiac output on the depressed and flattened ventricular function curve characteristic of impaired contractility. Importantly, vasodilator therapy possesses the ability to interrupt this deleterious sequence of events by partially counteracting the compensatory sympathetic reflex mechanism.[1]

Spectrum of Systemic Vasodilator Drugs

A variety of intravenous, oral, sublingual and cutaneous agents are now readily available which provide a spectrum of actions which result in the elevation of lowered cardiac output by reducing peripheral vascular resistance and/ or decline of increased ventricular end-diastolic volume (ventricular preload) by lowering venous tone. These drugs produce disparate modifications of cardiac function by their differing alterations of preload versus impedance, which are dependent upon their relative effects on systemic arteriolar resistance and venous capacitance vessels characteristic of each agent (Fig 5).[20] In addition, these drugs cause concomitant reduction in $M\dot{V}O_2$ which is of special importance in ischemic heart disease.

Therefore, modulation of cardiac function by the vasodilators is determined by their relative preload and impedance effects (Fig 6). Thus, the nitrates[15] principally cause venodilation (decrease elevated left ventricular end-diastolic pressure); nitroprusside,[21] phentolamine,[20] and prazosin[21] produce balanced arterial and venous dilation (decrease elevated left ventricular end-diastolic pressure and increase lowered cardiac output) provided left ventricular filling pressure is maintained at the upper limit of normal[12]; while hydralazine[13] predominantly effects arteriolar dilation (increases lowered cardiac output). With depressed cardiac output plus highly elevated left ventricular end-diastolic pressure and elevated peripheral vascular resistance, nitrates[15] also achieve some increase of lowered cardiac output by markedly reducing increased peripheral vascular resistance. Combined nitroprusside and dopamine[22] or dobutamine synergistically increase low cardiac output and decrease raised left ventricular end-dias-
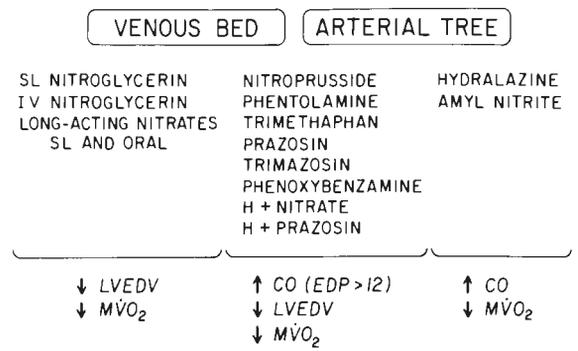

FIG 5—Diagram of the spectrum of actions of systemic vasodilators on the peripheral arterial tree and systemic venous bed. CO = cardiac output; EDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; $M\dot{V}O_2$ = myocardial oxygen consumption; IV = intravenous; SL = sublingual; H = hydralazine.
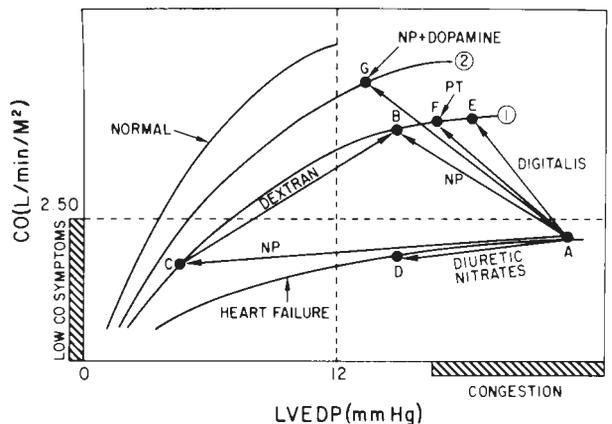

FIG 6—Relationship between cardiac output (CO) and left ventricular end-diastolic pressure (LVEDP) in a normal subject (left curve) and a patient with congestive heart failure (CHF) (right curve). Point A indicates the point of operation of the dysfunctioning left ventricle in CHF. The intermediate curve (1) is the improved relation between CO and LVEDP after the administration of digitalis (Point E), nitroprusside (NP) to above LVEDP of 12 mm Hg (Point B), and NP to below LVEDP of 12 mm Hg (Point C) with the addition of dextran (Point B). Prazosin and combined hydralazine-nitrate therapy are the same as NP from Point A to Point B. The enhanced CO and reduced LVEDP following the administration of phentolamine (PT) are shown by Point F. Hydralazine therapy can be represented from Point A to Point E. It is instructive that the improvements from Point A on the lowest ventricular function curve to Point B on the intermediate function curve (1) after NP administration and to Point F after PT was given are not the result of increased contractility; rather, they are due to the enhanced relation between CO and LVEDP that the reduction of impedance to left ventricular ejection NP and PT allow. Point D on the CHF curve is the LVEDP after diuretic or nitrate therapy. The intermediate curve (2) demonstrates the improvement in CO and decrease of LVEDP achieved with combined NP and dopamine therapy (Point G). The horizontal broken line indicates the lower limit of normal for CO and the vertical broken line indicates the upper limit of normal of LVEDP. Congestion = pulmonary congestion.

tolic pressure. Mechanical counterpulsation aids nitroprusside in acute myocardial infarction. The 30-minute venodilator action of sublingual nitroglycerin[23,24] is extended by 4 to 6 hours by cutaneous nitroglycerin ointment,[25] oral isosorbide dinitrate,[15] oral pentaerythritol tetranitrate,[26] and by sustained-release nitroglycerin capsules.[27] Ambulatory oral vasodilator therapy is provided by long-acting nitrates[15] (relieve pulmonary congestion); hydralazine[13] (improves fatigue); and prazosin alone,[16,28] combined nitrate-hydralazine,[29] and combined prazosin-hydralazine[5] (improve both dyspnea and fatigue).

Conclusions and Future Directions

Since activity of the renin-angiotensin system is increased in cardiac dysfunction,[2] angiotension II contributes in part to the increase of total peripheral vascular resistance characteristic of the heart failure state. Furthermore, this renin mechanism is stimulated in most instances of chronic systemic vasodilator therapy which attenuates systemic arteriolodilation produced by such treatment. Because recent evidence has been provided that administration of angiotensin-converting enzyme inhibitor in patients with heart failure results in dilation of the peripheral arterial bed with an increase in cardiac output and decrease in left ventricular filling pressure, considerable attention is now being focused on the efficacy of oral and intravenous converting enzyme inhibitors alone and in combination with conventional systemic vasodilators in clinical heart failure.[30] In addition, the vasodilator properties of the prostaglandins are also under evaluation in heart failure therapy.

The initial administration of the vasodilators to congestive heart failure patients is usually accompanied by a favorable diuresis. However, with prolonged use of the agents, body fluid accumulation often takes place, requiring greater dosage of concomitant diuretics. While oral furosemide is generally useful in this respect, the administration of spironolactone has been particularly beneficial in effecting diuresis,[31] probably caused by vasodilator-stimulation of the renin axis, resulting in increased aldosterone secretion.

With the prolonged use of each of the oral vasodilators in the ambulatory treatment of severe congestive heart failure, tolerance to the agents may develop in some individuals after several months. In the case of prazosin, tolerance can occur in approximately one third of patients after six months of effective therapy.[32] This tolerance is surmountable with a return of prazosin efficacy by increasing the dose of the drug, or by the brief discontinuation of the agent for a few weeks, or by switching for a short period to another vasodilator regimen such as trimazosin[33] or combined nitrate-hydralazine. Not a single instance of tachyphylaxis with repeated prazosin administration has been observed in over 150 heart failure patients to whom the agent has been given for either investigational or therapeutic purposes at our institution. The few reports of apparent prazosin tachyphylaxsis can each be readily attributed to faulty study design and/or incorrect interpretation such as those by Chatterjee,[34] Packer et al,[34] and Elkayam et al.[36] In contrast, the chronic use of hydralazine in heart failure, besides possible tolerance and the occasional side effects of the lupus erythematosus syndrome and peripheral neuropathy, may cause hydralazine-induced tachycardia, a frequent and serious complication,[37] leading to potentially lethal dysrhythmias, angina pectoris, and left ventricular pump deterioration.

The most important question as yet unanswered is the effectiveness of vasodilator therapy in acute and chronic refractory heart failure and in reducing complications and mortality. Although some preliminary studies have been encouraging, the definitive answers have not yet been established. If myocardial ischemia plays an important role in essential hypertension, cardiomyopathies and chronic coronary heart disease, then the increased ventricular filling pressures in these conditions probably contribute to sustained subendocardial ischemia with resultant progression of cardiac dysfunction.[1] Provided this mechanism is operative, then reduction of increased filling pressure by vasodilators should improve subendocardial perfusion and thereby diminish morbidity and extend longevity.

It is remarkable how quickly systemic vasodilator therapy has become established as an important new medical treatment for both acute and chronic heart failure.[19] Perhaps no other recent therapeutic concept in cardiovascular medicine has been so rapidly translated into practical clinical management as that of reducing left ventricular afterload by means of

vasodilator drugs. In our thinking about the management of congestive heart failure, it is apparent that a change of focus has occurred from emphasis on contractility prevalent in the past decade to innovative considerations of cardiac unloading by agents that primarily relax vascular smooth muscle without direct actions on the heart.[1] In consort, reexamination of the proper role of the digitalis glycosides is taking place.

Some clinicians maintain that the vasodilators are important as adjuncts in severe heart failure for use when traditional means are inadequate, to be added only in combination with digitalis and diuretics; others already view the vasodilators as equal or even better alternatives than the conventional agents. In the difficult circumstance of refractory acute or chronic heart failure, the combination 'of vasodilators and powerful cardiotonics such as dopamine (Fig 6) or dobutamine in hospital situations,[22] and digitalis[38] or promising new oral positive inotropics on the horizon in outpatient settings,[1] provide the most potent pharmacologic augmentation of pump function possible. It is probable in the future that as more experience is gained with the vasodilators and as newer agents become available, the systemic vasodilators will be utilized as frequently as digitalis in the standard treatment of congestive heart failure.

REFERENCES

1. MASON DT: Symposium on vasodilator and inotropic therapy of heart failure. Symposium perspective. *Am J Med* 65:101–105, 1978.

2. MASON DT, SPANN JF JR, ZELIS R, ET AL: Alterations of hemodynamics and myocardial mechanics in patients with congestive heart failure. *Progr Cardiovasc Dis* 12:507–557, 1970.

3. MASON DT: Regulation of cardiac performance in clini-

cal heart disease. *Am J Cardiol* 32:437–448, 1973.

4. MASON DT: *Congestive Heart Failure.* New York, Yorke Medical Books, 1976.

5. MASON DT: Afterload reduction and cardiac performance. *Am J Med* 65:106–125, 1978.

6. BURCH GE: Evidence for increased venous tone in chronic congestive heart failure. *Arch Int Med* 98:750–766, 1956.

7. JOHNSON JB, GROSS JF, HALE E: Effects of sublingual administration of nitroglycerin on pulmonary artery-pressure in patients with failure of the left ventricle. *N Engl J Med* 257:1114–1117, 1957.

8. MAJID PA, SHARMA B, TAYLOR SH: Phentolamine for vasodilator treatment of severe heart failure. *Lancet* 2:719–724, 1971.

9. FRANCIOSA JA, GUIHA NH, LIMAS CJ, ET AL: Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet* 1:650–654, 1972.

10. CHATTERJEE K, PARMLEY WW, GANZ W, ET AL: Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. *Circulation* 48:1183–1193, 1973.

11. CHATTERJEE K, PARMLEY WW, SWAN HJC, ET AL: Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvar apparatus. *Circulation* 48:684–690, 1973.

12. MILLER RR, VISMARA LA, ZELIS R, ET AL: Clinical use of sodium nitroprusside in chronic ischemic heart disease. *Circulation* 51:328–336, 1975.

13. CHATTERJEE K, PARMLEY WW, MASSIE B, ET AL: Oral hydralazine therapy for chronic refractory heart failure. *Circulation* 54:879–883, 1976.

14. MILLER RR, VISMARA LA, DEMARIA AN, ET AL: Afterload reduction therapy with nitroprusside in severe aortic regurgitation. *Am J Cardiol* 38:564–567, 1976.

15. WILLIAMS DO, BOMMER WJ, MILLER RR, ET AL: Hemodynamic assessment of oral peripheral vasodilator therapy in chronic congestive heart failure. *Am J Cardiol* 39:84–91, 1977.

16. AWAN NA, DEMARIA AN, MASON DT, ET AL: Efficacy of ambulatory systemic vasodilator therapy with oral prazosin in chronic refractory heart failure. *Circulation* 56:346–354, 1977.

17. AWAN NA, DEMARIA AN, MASON DT, ET AL: Beneficial effects of impedance reduction therapy in valvular heart disease. *Pract Cardiol* 4:179–186, 1978.

18. MILLER RR, AWAN NA, MASON DT: Nitroprusside ther-

apy in acute and chronic coronary artery disease. *Am J Med* 65:167–172, 1978.

19. MASON DT: Ventricular afterload reduction therapy in management of congestive heart failure. *Clin Cardiol* 2:55–59, 1978.

20. MILLER RR, VISMARA LA, WILLIAMS DO, ET AL: Pharmacological mechanisms for left ventricular unloading in clinical congestive heart failure. *Circ Res* 39:127–133, 1976.

21. AWAN NA, MILLER RR, MASON DT: Comparison of effects of nitroprusside and prazosin on left ventricular function and the peripheral circulation in chronic refractory congestive heart failure. *Circulation* 57:152–159, 1978.

22. MILLER RR, AWAN NA, JOYE JA, ET AL: Combined dopamine and nitroprusside therapy in congestive heart failure. *Circulation* 55:881–884, 1977.

23. MASON DT, BRAUNWALD E: The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 32:755–766, 1965.

24. DEMARIA AN, VISMARA LA, AUDITORE K, ET AL: Effects of nitroglycerin on left ventricular cavitary size and cardiac performance determined by ultrasound in man. *Am J Med* 57:754–760, 1974.

25. AWAN NA, MILLER RR, MAXWELL KS ET AL: Cardiocirculatory and antianginal actions of nitroglycerin ointment. *Chest* 73:14–18, 1978.

26. KLEIN RC, AMSTERDAM EA, PRATT C, ET AL: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy, abstract. *Clin Res* 26:243A, 1978.

27. AMSTERDAM EA, AWAN NA, DEMARIA AN, ET AL: Sustained salutary effects of oral controlled-release nitroglycerin on ventricular function in congestive heart failure. *Clin Cardiol* 2:19–25, 1979.

28. ARONOW WS, DANAHY DT: Efficacy of trimazosin and prazosin therapy on cardiac and exercise performance in outpatients with chronic congestive heart failure. *Am J Med* 65:155–160, 1978.

29. PIERPONT GL, COHN JN, FRANCIOSA JA: Combined oral hydralazine-nitrate therapy in left ventricular failure. *Chest* 73:8–13, 1978.

30. AWAN NA, HERMANOVICH J, SKINNER P, ET AL: Cardiocirculatory actions of the oral angiotensin-converting enzyme inhibitor, captopril, in severe chronic congestive heart failure, abstract. *Clin Res* 27:228A, 1979.

31. MANTLE JA, RUSSELL RO, ROGERS WJ, ET AL: Diuretic effect of isosorbide dinitrate in acute congestive heart failure. *Herz* 3:219, 1978.

32. AWAN NA, HERMANOVICH J, MASON DT, ET AL: Ambulatory prazosin treatment of chronic congestive heart failure: Development of tolerance and maintenance of salutary vasorelaxant actions by higher dosage, substitution and interrupted therapy. *Am J Cardiol*, in press.

33. AWAN NA, HERMANOVICH J, MASON DT, ET AL: Cardiocirculatory effects of afterload reduction with oral trimazosin in severe chronic congestive heart failure. *Am J Cardiol*, in press.

34. CHATTERJEE K: Chronic congestive heart failure and vasodilator therapy. *J Cont Ed Cardiol* 13:17–29, 1978.

35. PACKER M, GORLIN R, HERMAN MV: Hemodynamic and clinical tachyphylaxis to prazosin mediated afterload reduction in severe chronic congestive heart failure. *Circulation* 59:531–539, 1979.

36. ELKNYAM U, LEJEMTEL T, MITLESH M, ET AL: Marked early attenuation of hemodynamic effects of oral prazosin therapy in chronic congestive heart failure, abstract. *Am J Cardiol* 43:403, 1979.

37. LASLETT L, DEMARIA AN, AMSTERDAM EA, ET AL: Hydralazine-induced tachycardia and sodium retention in heart failure. *Arch Int Med* 138:819–820, 1978.

38. MASON DT: Digitalis pharmacology and therapeutics: Recent advances. *Ann Int Med* 80:520–530, 1974.