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MEDICAL GRAND ROUNDS

CHRONIC CONGESTIVE HEART FAILURE: THE NATURE OF THE PROBLEM AND ITS MANAGEMENT IN 1984

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"The very essence of cardiovascular practice is recognition of early heart failure and discrimination between different grades of failure."

Sir Thomas Lewis (1933)

I. DEFINITION

Heart failure is the pathophysiological state in which an abnormality of cardiac function results in a failure of the heart to pump blood at a rate commensurate with the metabolic requirements of the body. This is frequently, but not invariably, due to a defect in myocardial contraction, i.e., *myocardial failure.*

It is important to appreciate that not all patients with congestive cardiac failure have myocardial failure. In such cases, heart failure occurs because the normal heart is faced with an excessive load, that exceeds compensatory mechanisms, or because ventricular filling is impaired. Conversely, myocardial failure (in the early stages) may be present without overt congestive heart failure; the latter only occurs once myocyte dysfunction is far advanced and compensatory mechanisms, including chamber dilatation, vasoconstriction and fluid retention, come into play.

It is also important to recognize at the outset that the diagnosis of congestive cardiac failure is frequently made in error: excessive salt and water retention with resultant circulatory congestion (primarily due to hepatic or renal disorders) may occur in the absence of any cardiac abnormality and mimic the clinical features of congestive heart failure. It may be necessary under these circumstances to obtain an objective assessment of cardiac pump function in order to plan rational therapy.

II. MAGNITUDE OF THE PROBLEM

Congestive heart failure is a common ailment with a variety of causes. An estimated 3.5 to 4 million Americans have chronic congestive heart failure (Weber, 1982). Hospital statistics indicate that 2 per 1,000 persons in the general population are admitted to the hospital in cardiac failure while approximately 20 per 1000 visit physicians for cardiac failure one or more times a year (Klainer et al, 1965). More recent data from the Framingham study (Kannel et al, 1982) suggest that the incidence (i.e., the number of new cases per year) averages 3.7 per 1000 for men and 2.5 per 1000 for women. The incidence of cardiac failure more than doubles each decade from 45 to 75 years (Table I).

In the Framingham study, hypertension preceded cardiac failure in 75 percent of cases. This finding is somewhat surprising. Although coronary artery disease cases developed cardiac failure at 10 times the rate of the general population, coronary artery disease, unaccompanied by hypertension, occurred before cardiac failure in only 10 percent. Diabetic women had a 5-fold increased incidence of congestive failure and diabetic men had a 2-fold greater risk than non-diabetics. The risk of congestive failure tended to increase with the level of blood sugar. In this country, valvular heart disease now causes less than 10 to 20 percent of cases of cardiac failure.

Congestive heart failure is one of the most common conditions encountered in Parkland Memorial Hospital. In 1982, 274 patients were admitted with a primary diagnosis of congestive heart failure and 24 died due to this condition.

TABLE I

AVERAGE ANNUAL INCIDENCE OF CARDIAC FAILURE:
20 YEAR FOLLOW-UP

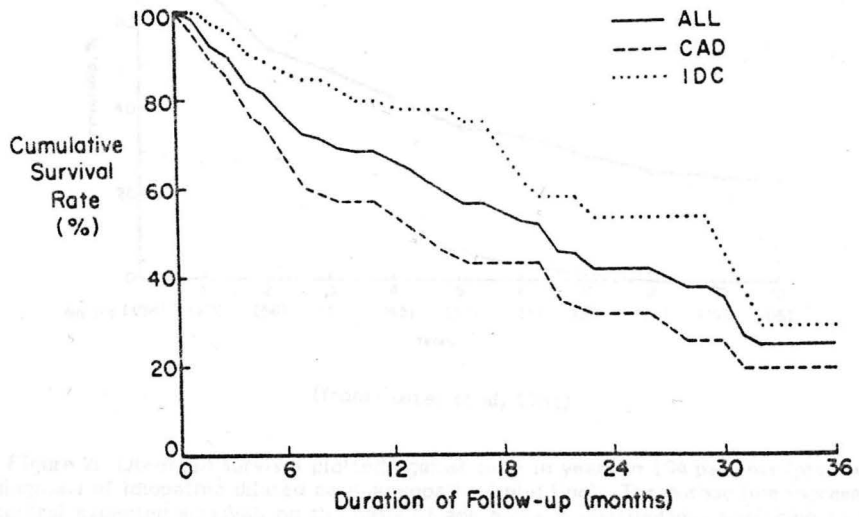
	Rate per 1000	
Age	Men	Women
45-54	1.8	0.8
55-64	4.3	2.7
65-74	8.2	6.8
Total	3.7	2.5

(from Kannell et al, 1982)

III. PROGNOSIS OF PATIENTS WITH CONGESTIVE HEART FAILURE

Congestive heart failure is a highly fatal disorder with a 5 year survival rate well below 50 percent, which is worse than that observed for cancer in general. The Framingham study (Kannel et al, 1982) found that the probability of death within 4 years of onset of overt cardiac failure was 52 percent for men and 34 percent for women.

At the present time, the major causes of congestive heart failure (once surgically remediable conditions have been excluded) encountered in clinical practice are coronary artery disease and so-called "idiopathic dilated (congestive) cardiomyopathy." Idiopathic dilated cardiomyopathy is a clinical diagnosis by exclusion and almost certainly comprises many different pathological entities that are not yet defined. Franciosa et al (1983) have provided detailed follow-up on 182 patients with chronic left ventricular failure who were symptomatic despite therapy. The cause of congestive heart failure was coronary artery disease in 95 and idiopathic dilated cardiomyopathy in 87 patients. The overall mortality rate was 34 percent at 1 year, 59 percent at 2 years, and 76 percent at 3 years. The mortality rate in patients with coronary artery disease was 46 percent and 69 percent at 1 and 2 years, respectively, compared to 23 percent and 48 percent at 1 and 2 years in those with idiopathic dilated cardiomyopathy ($p < 0.01$) (Figure 1).

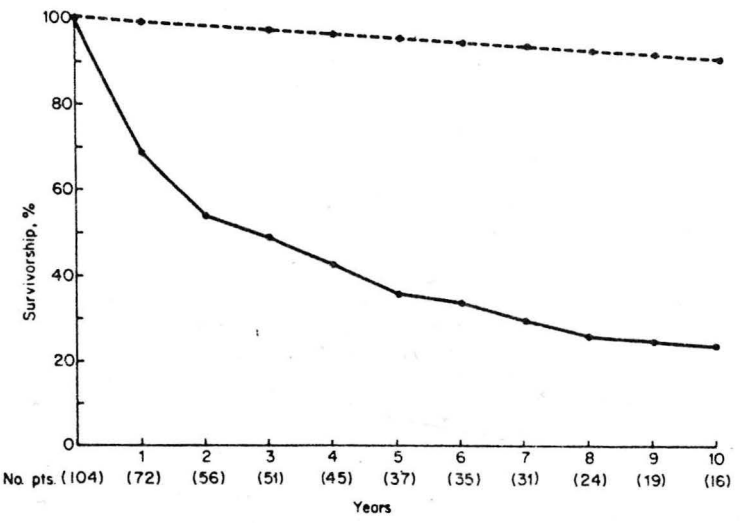


(from Franciosa et al, 1983)

Figure 1: Survival curves in patients with severe chronic left ventricular failure due to cardiomyopathy. The curves for coronary artery disease (CAD) and idiopathic dilated cardiomyopathy (IDC) groups are significantly different ($p < 0.01$). ALL = all patients (CAD + IDC).

In a recent study from the Mayo Clinic (Fuster et al, 1983), 104 patients with idiopathic dilated cardiomyopathy were followed for 6 to 20 years (Figure 2). The survival rate is very similar to that reported by Franciosa et al (1983).

In the total group of patients reported by Franciosa et al (1983), at the time of entry into the study, the non-survivors (n = 88) were more symptomatic, had lower mean arterial pressure, higher left ventricular filling pressure, lower cardiac index, lower stroke volume, higher systemic vascular resistance, and lower stroke work than the survivors (n = 94) (Table II).



(from Fuster et al, 1981)

Figure 2: Observed survival plotted against time in years in 104 patients (pts.) with the diagnosis of idiopathic dilated cardiomyopathy (solid line). The dashed line represents the control expected survival, on the basis of age and sex distribution, according to the death rates of the Minnesota 1970 White Population Life Table. The number of alive patients under observation at each follow-up interval is indicated in parentheses.

TABLE II

BASELINE CHARACTERISTICS OF PATIENTS WITH SEVERE CHRONIC LEFT VENTRICULAR FAILURE DUE TO CARDIOMYOPATHY

	Nonsurvivors (n = 88)	Survivors (n = 94)	p
Age (yr)	57 ± 10	56 ± 8	NS
Duration of symptoms (mo)	45 ± 43	39 ± 27	NS
Clinical class (NYHA)	3.3 ± 0.6	2.9 ± 0.6	<0.001
Heart rate (beats/min)	87 ± 15	83 ± 16	NS
Mean arterial pressure (mmHg)	87 ± 13	94 ± 13	<0.001
Left ventricular filling pressure (mmHg)	29 ± 7	24 ± 9	<0.001
Cardiac index (liters/min/m^2)	2.0 ± 0.7	2.5 ± 0.8	<0.001
Stroke volume (ml/beat)	45 ± 16	59 ± 5	<0.001
Systemic vascular resistance (units)	25 ± 10	21 ± 8	< 0.01
Stroke work (g-m)	35 ± 19	56 ± 33	<0.001

Values are listed as mean ± standard deviation.
NYHA = criteria of the New York Heart Association; NS = not significant.

(from Franciosa et al, 1983)

This study may at first sight seem to be an unnecessary statement of the obvious, namely, that the patients with the most severe cardiac failure are the most likely to die. However, the recent demonstration of a lack of correlation between resting hemodynamic measurements and exercise capacity in patients with congestive heart failure has raised questions about the value of such measurements (Franciosa et al, 1981). Clearly, hemodynamic measurements do relate to prognosis in these patients and their use is of value because their modification may conceivably alter prognosis. Earlier studies (Hatle et al, 1976a,b; Fuster et al, 1981) have also demonstrated a relationship between clinical and radiographic signs, left ventricular function, and prognosis.

A disturbing facet of the problem of chronic congestive heart failure is the observation that approximately half the deaths occur suddenly and are not due to pump failure per se (Franciosa et al, 1983; Wilson et al, 1983a). However, the major reason for sudden-death is in dispute. The study by Fuster et al (1981) of patients with idiopathic dilated cardiomyopathy noted an 18 percent (33 percent in patients with atrial fibrillation and 14 percent in those in sinus rhythm) incidence of systemic emboli. No embolic events occurred in patients on anticoagulant therapy. Likewise, malignant arrhythmias occur commonly in patients with severe congestive heart failure. In a recent study of 77 patients with severe heart failure (NYHA Class III and IV) followed for 12 $\pm$ 11 months reported by Wilson et al (1983a), Holter monitoring showed a high incidence of ventricular premature depolarizations which were paired in 62 percent, multiform in 71 percent, 3 or more consecutive in 51 percent, and 5 or more in 39 percent. Cardiac mortality (52 percent at 1 year) was due equally to sudden death and heart failure. Cardiac mortality during the first 4 months was related by univariate analysis to functional class ($X^2 = 11.4$; $p < 0.001$) and to the presence of 5 or more consecutive ventricular premature depolarizations ($X^2 = 3.9$; $p < 0.05$) due to a relation between these variables and *non-sudden* death; *sudden* death was not related to any initial variable. Multivariate analysis identified only functional class as an independent prognostic variable, which was a predictor of non-sudden death. These findings are in striking contrast to the finding in the MILIS study that the degree of ventricular ectopy and the degree of left ventricular dysfunction are *independent* early predictors of survival in patients following an acute myocardial infarction (Mukharji et al, 1983).

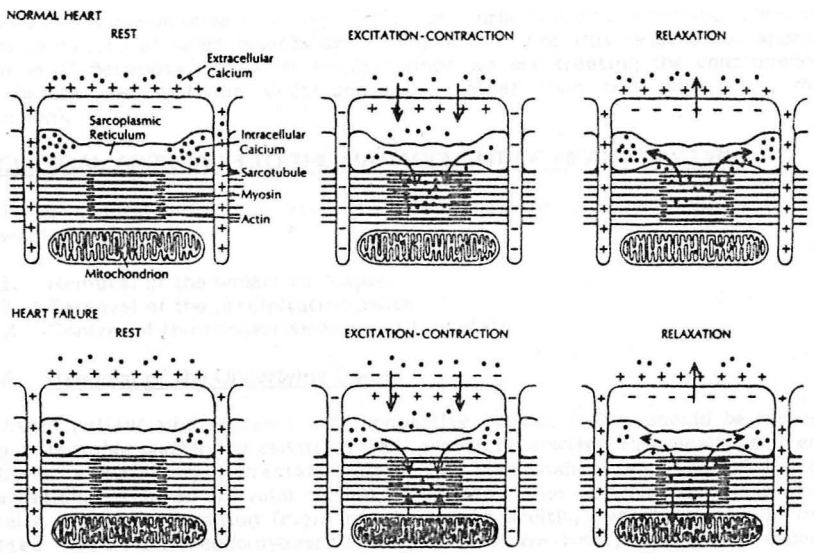
Clearly, more information is needed concerning the etiology of sudden death, and its prevention in patients with congestive heart failure, if we are to make any impression on survival in patients with this clinical problem.

IV. WHAT IS THE PATHOLOGICAL BASIS FOR MYOCARDIAL FAILURE

Conceptually, myocardial failure occurs when: (1) there is a *quantitative* lack of myocardial cells, due to destruction (e.g., infarction) or replacement (e.g., amyloid and other infiltrative disorders) of the normal myocardial architecture and/or (2) there is a *qualitative* defect in the myocardial cells.

Myocardial failure usually develops slowly and is generally preceded by a stage in which either the entire heart, or the residual viable portion of an otherwise damaged heart, hypertrophies without failure (Cooper, 1982). This intermediate condition of stable cardiac hypertrophy permits compensation of variable extent and duration for myocardial injury or hemodynamic overload. A question of fundamental importance is why initial compensatory hypertrophy so frequently ultimately results in myocardial failure. Available evidence suggests that it is not the increased size of the myocytes per se but rather some alteration in their function that is responsible for this course of events. Whether the alteration in function is due to an abnormality (or abnormalities) in energy production, or in the contractile process, is unclear. The present evidence suggests that

the problem is not due to defective energy production but rather due to an abnormality in the contractile process. One postulated mechanism (Chidsey, 1975) suggests that the primary defect resides in the sarcoplasmic reticulum of the myocyte (Figure 3). According to this theory, a primary defect in the sarcoplasmic reticulum leads to reduced calcium stores at rest, with an increased mitochondrial calcium content. With excitation, less calcium is released by the sarcoplasmic reticulum in heart failure, and some calcium may be released from the large mitochondrial store. Relaxation also proceeds more slowly with failure, since the uptake of calcium into the sarcoplasmic reticulum is reduced. Theoretically, defective calcium transport could interrupt maximal excitation-contraction coupling by several mechanisms: decreased calcium availability at the sarcolemma; decreased calcium transport across this membrane; altered calcium release or uptake by the intracellular sarcoplasmic reticulum (as proposed by Chidsey, 1975); or decreased calcium availability and/or removal from contractile protein (Tilton et al, 1983). The latter two mechanisms appear the more likely in view of the reduced rate of relaxation seen in some models of heart failure. The various pathogenetic mechanisms are not necessarily mutually exclusive. Thus, it may be that alterations in the contractile process and in energy production by oxidative phosphorylation are both important, or important to a variable degree in different settings. The difficulty of relating in vitro biochemical findings to abnormalities in vivo have been well summarized by Entman et al (1982).



(from Chidsey, 1975)

Figure 3: The postulated changes in mitochondrial and sarcoplasmic reticulum uptake and release of calcium that occur in heart failure.

The intrinsic abnormalities in myocyte function may be aggravated by a variety of other factors, including depletion of cardiac norepinephrine stores, down-regulation of myocardial beta-adrenergic receptors, and possibly even microvascular spasm with resultant further cellular necrosis. Chidsey et al (1963) were the first to describe diminished myocardial norepinephrine content in patients with heart failure. Animal models of heart failure have confirmed these observations and demonstrated depressed cardiac inotropic and chronotropic responses after sympathetic nerve stimulation (Covell et al, 1966). In addition, Bristow et al (1982) have demonstrated a decrease in catecholamine sensitivity and beta-adrenergic receptor density in failing human hearts. The reduction in myocardial norepinephrine stores in conjunction with the down-regulation in beta-adrenergic receptors deprive the failing myocardium of the benefit of an important compensatory mechanism, namely, the increase in circulating catecholamines that occurs in heart failure. Finally, microvascular spasm may play a role in the pathogenesis of at least some forms of myocardial failure (Sonnenblick, 1982). There is some evidence that this is an important phenomenon in the Syrian hamster model of heart failure and that it may be of pathogenetic importance in alcohol-associated cardiac decompensation. It is of some interest that this microvascular spasm can be prevented by treatment with verapamil. This raises the intriguing possibility that calcium antagonists may have a role to play in the very early stages of some forms of myocardial dysfunction. Willerson (1982) and Tilton et al (1983) from this institution have recently provided succinct reviews of the various aspects of this complex and confusing subject.

In summary, our understanding of the structural and/or biochemical abnormalities that cause failure of heart muscle are rudimentary. For this reason, our approach to therapy is of necessity somewhat empiric since we are treating the *consequence* (i.e., pump failure and systemic decompensation) rather than the *cause* (i.e., myocyte dysfunction).

V. CLINICAL APPROACH TO THE MANAGEMENT OF HEART FAILURE

Three general principles apply to the treatment of heart failure (Smith and Braunwald, 1984):

1. Removal of the underlying cause
2. Removal of the precipitating cause
3. Control of the congestive heart failure state

A. Removal of the Underlying Cause:

Every patient who presents with congestive cardiac failure should be suspected of having a treatable underlying condition until proven otherwise. Practically, this entails a search for a surgically correctable structural abnormality (e.g., congenital cardiac malformation, acquired valvular lesion, localized large ventricular aneurysm) or a medically treatable condition (e.g., infective endocarditis, hypertension). In cases of suspected myocarditis, endomyocardial biopsy is a low-risk procedure in experienced hands and is mandatory before instituting corticosteroid and/or immunosuppressive therapy (Mason, 1978). In general, the younger the patient and the shorter the history (under 6 months) the higher one's index of suspicion should be for a diagnosis of myocarditis. Endomyocardial biopsy may also occasionally be of value in detecting specific muscle diseases, amyloidosis, sarcoidosis and in distinguishing between a restrictive cardiomyopathy and constrictive pericarditis.

B. **Removal of the Precipitating Cause:**

The recognition, prompt treatment and, if possible, prevention of precipitating factors that produce or exacerbate heart failure are critical to successful management of congestive cardiac failure. Common precipitating factors include:

1. inappropriate reduction of therapy or dietary excesses of sodium
2. tachy or bradyarrhythmias
3. systemic infection
4. pulmonary embolism
5. physical, environmental and emotional excesses
6. high-output states (anemia, pregnancy, thyrotoxicosis, arteriovenous malformations, Paget's disease, beri-beri)
7. administration of a cardiac depressant or salt-retaining drug (alcohol, beta-adrenergic blocking agents, disopyramide, calcium antagonists, adriamycin, cyclophosphamide, estrogens, androgens, corticosteroids, nonsteroidal antiinflammatory agents)
8. development of a second form of heart disease (e.g., acute myocardial infarction, acute rupture of chordae tendineae or papillary muscle)
9. development of an unrelated illness (e.g., renal failure, hepatic failure, prostatic obstruction)
10. injudicious intravenous fluid administration

C. **Control of the Congestive Heart Failure State:**

Control of the congestive heart failure state may be divided conceptually into 3 categories (Table III):

1. Improvement of the heart's pumping performance: efforts to restore the pump function ("contractility") of the failing heart toward normal.
2. Reduction of heart's workload: reduction of the demands placed on the heart to generate pressure and/or pump blood.
3. Control of excessive salt and water retention: salt and water restriction, diuretics, and mechanical removal of fluid.

A condition as variable in its severity, manifestations and setting cannot be treated according to a simple formula. Nevertheless, a stepwise strategy of management is helpful and will serve as a useful introduction to a detailed consideration of the pros and cons of each of the treatment modalities. Such a stepwise strategy of treatment is outlined on the next page (modified after Smith and Braunwald, 1984).

The therapeutic strategy outlined in Table IV and Figure 4 presents a stepwise approach to the management of the patient with congestive heart failure, once surgically remediable causes have been excluded. In mild congestive heart failure, avoidance of strenuous physical activity may be all that is necessary. Weight reduction, when possible, is equally important. If this is insufficient, mild salt restriction or the addition of a thiazide diuretic may be necessary. If symptoms persist despite this therapy, it may be necessary to proceed to more aggressive medical therapy.

TABLE III

CONTROL OF CONGESTIVE HEART FAILURE

1. **Improvement of Pumping Performance**
   - (A) Digitalis glycoside
   - (B) Sympathomimetic agents
   - (C) Other positive inotropic agents
   - (D) Pacemaker
2. **Reduction of Workload**
   - (A) Physical and emotional rest
   - (B) Treatment of obesity
   - (C) Vasodilator therapy
   - (D) Assisted circulation
3. **Control of Excessive Salt and Water Retention**
   - (A) Low-sodium diet
   - (B) Diuretics
   - (C) Mechanical removal of fluid
     - (1) Thoracentesis
     - (2) Paracentesis
     - (3) Dialysis
     - (4) Phlebotomy

(from Smith and Braunwald, 1984)

TABLE IV

OUTLINE OF TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE*

1. **Restriction of Physical Activity**
   - (A) Discontinue exhausting sports and heavy labor
   - (B) Discontinue full-time work or equivalent activity, introduce rest periods during the day
   - (C) Confine to house
   - (D) Confine to bed-chair
2. **Restriction of Sodium Intake**
   - (A) Eliminate saltshaker at table (Na = 1.6 to 2.8 gm)
   - (B) Eliminate salt in cooking and at table (Na = 1.2 to 1.8 gm)
   - (C) Institute A and B above plus low-sodium diet (Na = 0.2 to 1.0 gm)
3. **Diuretics**
   - (A) Moderate diuretics (thiazide)
   - (B) "Loop" diuretic (ethacrynic acid or furosemide)
   - (C) "Loop" diuretic plus metolazone (2.5 to 10 mg/day)
   - (D) "Loop" diuretic plus metolazone (5 to 10 mg/day) and distal tubular diuretic
4. **Digitalis**
   - (A) Maintain serum level at 0.8 to 1.5 ng/ml
5. **Vasodilation**
   - (A) Captopril or isosorbide dinitrate
   - (B) Intravenous nitroprusside
6. **Other Inotropic Agents** (Dopamine, dobutamine)
7. **Special Measures** (thoracentesis, paracentesis, dialysis, assisted circulation, cardiac transplantation)

*Numbers and letters correspond to Figure 4.

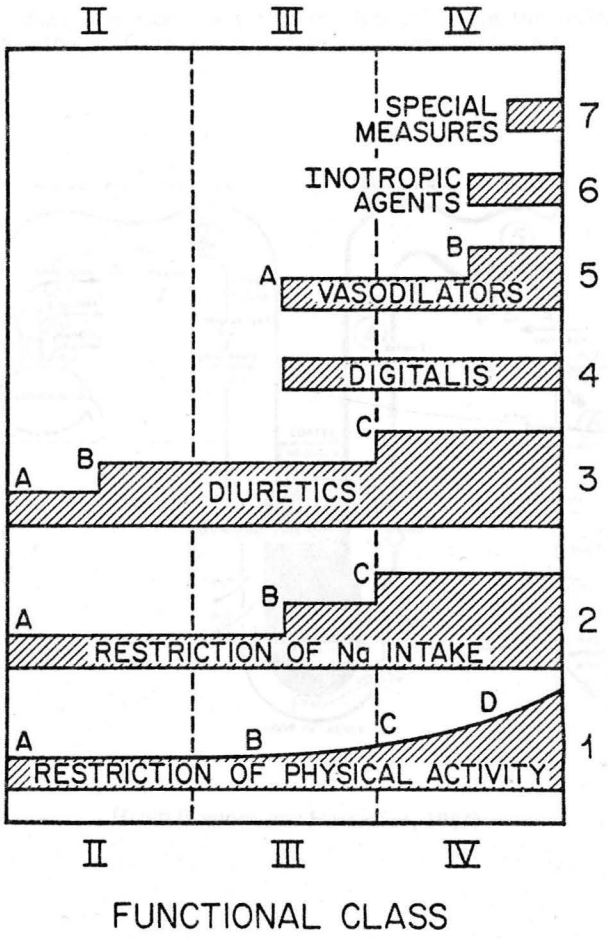
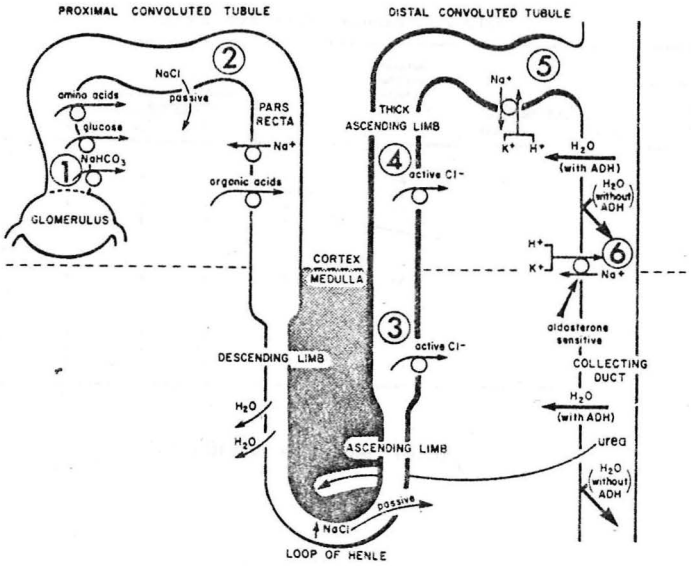


Figure 4: Strategy of treatment of chronic congestive heart failure in the adult. Various modes of therapy and the intensity of their application at various stages of the patient's course are plotted. For further explanation, see Table IV.

VI. DIURETICS

Diuretics form the cornerstone of management of congestive heart failure. Very few patients are refractory to medical therapy with diuretics if these agents are used judiciously in conjunction with sodium restriction.

The sites of diuretic action are shown in Figure 5, while the relative potency of various diuretics and their effects on electrolyte excretion are indicated in Table V.



(from Brenner and Hostetter, 1983)

Figure 5: The sites of diuretic action, shown as circled numbers, are as follows:

Site 1: Proximal tubule. Sensitive to inhibitors of carbonic anhydrase.

Site 2: Proximal tubule. An osmotic diuretic acting at this site results in *increased* free-water production and *increased* potassium loss.

Site 3: Medullary diluting segment of ascending limb. A diuretic acting at this site results in *decreased* free-water production and *increased* potassium loss.

Site 4: Cortical diluting segment of ascending limb. A diuretic acting at this site results in *decreased* free-water production and *increased* potassium loss.

Site 5: Aldosterone-insensitive portion of distal tubule. A diuretic acting at this site produces *decreased* potassium loss.

Site 6: Aldosterone-sensitive portion of distal tubule. A diuretic acting at this site produces *decreased* potassium loss but acts only in the presence of aldosterone.

TABLE V

EFFECTS OF DIURETICS ON ELECTROLYTE EXCRETION

Agent	Changes in Urinary Electrolytes				Maximal Fractional Excretion of Sodium (%)	Inhibitory Factors		Site(s) of Action (See Figure 4 for Site Numbers)
	Na^+	K^+	Cl^-	HCO_3^-		Acidosis	Alkalosis	
Weak Diuretics								
Acetazolamide	↑	↑	↑	↑	~4	+		1
Spironolactone	↑	↑	↑	↑	~2			6
Triamterene	↑	↑	↑	↑	~2			5
Amiloride	↑	↑	↑	↑	~2			5
Moderately Effective Diuretics								
Thiazide compounds (including metolazone)	↑	↑	↑	↑	~8			4
Potent Diuretics								
Organomercurials	↑	↑	↑		~20		+	3,4
Furosemide	↑	↑	↑		~23			3,4
Ethacrynic acid	↑	↑	↑		~23			3,4?,5,6

(from Brater and Thier, 1978)

Diuretics are agents that increase urinary excretion of salt and water. Thiazide diuretics can increase the fractional excretion of sodium by approximately 8 percent and are useful as first-line therapy for congestive heart failure. However, thiazides are generally ineffective in patients with renal insufficiency (glomerular filtration rate < 30 ml/min) and in themselves reduce renal blood flow (Heinemann et al, 1959) and are not of much value in severe congestive heart failure.

Once fluid retention becomes more severe, more potent "loop-diuretics," such as furosemide or ethacrynic acid, which can increase the fractional excretion of sodium approximately 23 percent (Table V) become necessary. These agents are equipotent but furosemide in large doses is less likely to cause permanent ototoxicity and gastrointestinal disturbance than ethacrynic acid. Both agents have a 6 to 8 hour duration of action when given orally (and 2 to 3 hours when given intravenously). It is therefore both logical and clinically efficacious to administer these agents in divided dosages in order to optimize their effects. Thus, a dosage of furosemide of 80 to 160 mg b.i.d. or t.i.d. is not unusual in patients with severe congestive heart failure. Clinical experience suggests that a daily dosage of furosemide much in excess of 400 mg/day is unlikely to promote a substantial further diuresis. *It is extremely important to appreciate that in patients with marked fluid retention, large oral doses of furosemide or ethacrynic acid may be ineffective while much smaller intravenous doses may promote a brisk diuresis.*

An alternative approach in the patient with marked fluid retention despite large doses of "loop-diuretics" is the use of metolazone in conjunction with furosemide. Metolazone (zaroxolyn) is a quinethazone derivative whose site of action and potency are similar to those of chlorothiazide (Steinmuller and Puschett, 1972: Fernandez and Puschett, 1973) when used alone. However, unlike most thiazides, metolazone is effective in patients with markedly reduced renal function (Craswell et al, 1973) and has a much longer duration of action, namely 24 to 48 hours (Steinmuller and Puschett, 1972). When used in combination with furosemide, it has a marked synergistic effect (Gunstone et al, 1971; Ram and Reichgott, 1977; Epstein et al, 1977; Oster et al, 1983). *The addition of small quantities of metolazone (e.g., 2.5 mg daily or alternate daily) in patients on large doses of furosemide may lead to a marked diuresis and profound hypokalemia unless the patient is monitored very closely.* For these reasons, combination therapy should preferably be commenced in-hospital in order to allow appropriate dosage adjustment.

Common complications of diuretic therapy with the agents mentioned include potassium depletion, metabolic alkalosis, hyponatremia, hyperuricemia, carbohydrate intolerance and ototoxicity. Hypokalemia is an ever-present hazard and mandates continual potassium repletion with oral potassium supplements. This is particularly true when metolazone is used. In some patients, it may be impossible to provide adequate potassium supplementation. In these cases, the addition of spironolactone may be particularly useful. Since ventricular ectopic activity is a common occurrence in patients with severe cardiac dysfunction, the risk of producing or increasing arrhythmias in these patients with diuretic therapy is of major concern (Holland et al, 1981). Metabolic alkalosis (contraction alkalosis) usually responds to a reduction in the diuretic dose and potassium supplementation. Occasionally, a brief period of therapy with acetazolamide, a carbonic-anhydrase inhibitor, may be necessary. Hyponatremia generally responds to restriction of fluid intake.

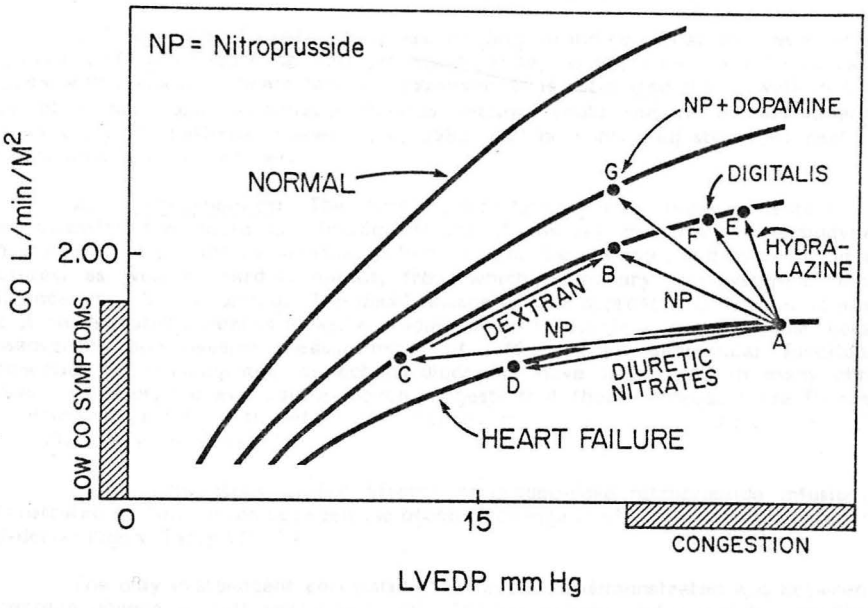
VII. VASODILATORS AND INOTROPIC AGENTS

A. Theoretical Concepts:

Before proceeding to a detailed consideration of the current status of vasodilator therapy in congestive heart failure, it is necessary to outline briefly a conceptual framework for the use of diuretics, vasodilators and inotropic agents. Although the biochemical derangements in the cardiac myocyte are poorly understood, the major hemodynamic derangements that characterize heart failure have been appreciated for some time. First, the Starling relationship (the relationship between the degree of "stretch" of the left ventricular muscle fibers and the output from the left ventricle) is markedly depressed (Figure 6), and second, there is a marked increase in systemic vascular resistance (aortic input impedance) due to a combination of increased vasoconstrictor drive, decreased vasodilator drive and fluid in the vessel walls, which further aggravates the situation by increasing the load against which the heart has to pump. This subject will not be discussed in any further detail since it has recently been reviewed in Grand Rounds by Dr. Gunnar Blomqvist (1983).

Figure 6 illustrates the traditional concepts concerning the effect of left ventricular preload reduction (diuretics, nitrates), afterload reduction (hydralazine), combined preload and afterload reduction (nitroprusside), inotropic therapy (digitalis), and combined vasodilatation and inotropic therapy (nitroprusside and dopamine). The terms left ventricular "preload" and "afterload" are commonly used to describe the degree of stretch of the left ventricle and the opposition to left ventricular ejection, respectively. This

figure is of necessity oversimplified since it is clear that there is no agent that is a pure afterload reducing agent or a pure preload reducing agent: both nitrates and diuretics (Wilson et al, 1981) may result in a reduction in afterload, and afterload-reducing agents also ultimately cause a reduction in preload. Nevertheless, *a key feature of this diagram is that an increase in cardiac output (associated with a reduction in left ventricular filling pressure) may occur either due to positive inotropic therapy or due to afterload reduction, or both.*



(after Mason, 1978)

Figure 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. NP = nitroprusside; Hy = hydralazine.

B. Assessment of the Efficacy of Vasodilator or Inotropic Therapy:

The *acute* benefit of vasodilator or inotropic therapy (particularly with agents such as nitroprusside, dopamine or dobutamine) in altering hemodynamics has been amply demonstrated and will not be discussed here. By 1978, there were some 600 articles and abstracts relating to this subject alone.

The *chronic* efficacy of vasodilator or inotropic therapy in patients with chronic congestive heart failure is much more contentious. Three end-points need to be considered, namely, the effect of therapy on *survival, hemodynamics and symptomatic status* (or exercise capacity). In addition, when considering the effects of therapy, it is extremely important to use *objective* measurements and a *double-blind, placebo-controlled study* design whenever possible to limit observer bias.

1. Survival: To date, there are no data to indicate that any vasodilator (or combination of vasodilators) or inotropic agent per se has improved the survival rate of patients with congestive heart failure. However, it is estimated that a well-controlled study of a particular vasodilator in this setting would require an enrollment of approximately 200 patients (Fisher et al, 1982) and no controlled study yet performed begins to approach this number.

2. Hemodynamics: The most reliable hemodynamic measurements to make when assessing the acute or chronic effects of therapy are *invasive* hemodynamic measurements of pulmonary arterial, pulmonary capillary wedge, and systemic arterial pressures, as well as cardiac output, from which pulmonary and systemic vascular resistances may be calculated. The disadvantage of this approach for chronic studies is that it necessitates repeated invasive studies which the patient may find unacceptable. Consequently, non-invasive measurements of left or right ventricular function by radionuclide ventriculography or echocardiography have been used in many chronic studies. However, the available evidence suggests that these techniques are frequently not sufficiently sensitive to detect the changes produced by vasodilator therapy (Firth et al, 1982; Haq et al, 1982).

In a recent study of the effects of graded-dose nitroprusside infusion, we demonstrated no correlation between the *absolute* change in invasive and multigated blood pool-derived data (Table VI).

The only independent correlation that could be demonstrated was between the *percentage* change in left ventricular end-diastolic volume index and the *percentage* change in pulmonary capillary wedge pressure (Table VII).

Although the correlation between these two variables is acceptable ($r = 0.68$; $p = 0.01$), the large negative intercept (in Figure 7) implies that a reduction in pulmonary capillary wedge pressure of more than 30 percent might occur without a change in end-diastolic volume index.

3. Symptomatic Status: The evaluation of a change in symptomatic status based purely on questioning of the patient may be extremely misleading. Therefore, uncontrolled studies that purport to demonstrate a marked subjective improvement due to a specific agent should be treated with great skepticism.

TABLE VI

RELATIONS BETWEEN ABSOLUTE CHANGES IN INVASIVE AND MULTIGATED BLOOD POOL DATA

	ΔTHDCI	ΔPCW	ΔPA	ΔFA	ΔTPVR	ΔTSVR
ΔLVEF	r = 0.53 NS	r = -0.14 NS	r = 0.07 NS	r = -0.01 NS	r = 0.01 NS	r = -0.14 NS
ΔLVEDVI	r = -0.55 NS	r = 0.53 NS	r = 0.46 NS	r = -0.08 NS	r = 0.35 NS	r = 0.14 NS
ΔLVESVI	r = -0.39 NS	r = 0.43 NS	r = 0.34 NS	r = -0.15 NS	r = 0.34 NS	r = 0.12 NS
ΔSCAN CI	r = 0.16 NS	r = 0.57 p = 0.05	r = 0.54 NS	r = 0.10 NS	r = 0.32 NS	r = 0.01 NS

Δ = absolute change; FA = mean femoral arterial pressure; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NS = not significant; PA = mean pulmonary arterial pressure; PCW = mean pulmonary capillary wedge pressure; r = correlation coefficient; SCAN CI = cardiac index by multigated blood pool scan; THDCI = thermodilution cardiac index; TPVR = total pulmonary vascular resistance; TSVR = total systemic vascular resistance.

(from Firth et al, 1982)

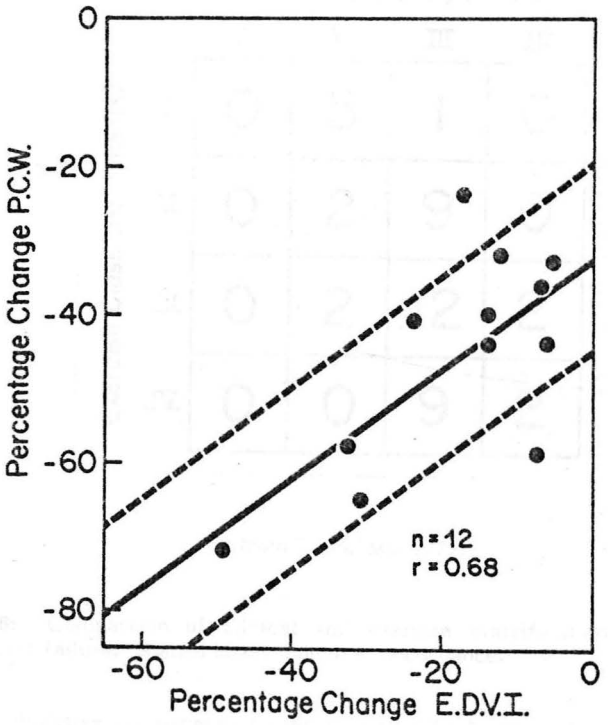
TABLE VII

RELATION BETWEEN PERCENT CHANGES IN INVASIVE AND MULTIGATED BLOOD POOL DATA

	%ΔTHDCI	%ΔPCW	%ΔPA	%ΔFA	%ΔTPVR	%ΔTSVR
%ΔLVEF	r = 0.41 NS	r = -0.16 NS	r = -0.01 NS	r = -0.07 NS	r = -0.19 NS	r = -0.30 NS
%ΔLVEDVI	r = -0.29 NS	**r = 0.68** **p = 0.01**	r = 0.43 NS	r = 0.16 NS	r = 0.44 NS	r = 0.26 NS
%ΔLVESVI	r = -0.15 NS	r = 0.60 p = <0.05	r = 0.35 NS	r = 0.01 NS	r = 0.38 NS	r = 0.13 NS
%ΔSCAN CI	r = 0.13 NS	r = 0.32 NS	r = 0.42 NS	r = -0.01 NS	r = 0.32 NS	r = -0.08 NS

Abbreviations as in Table VI.

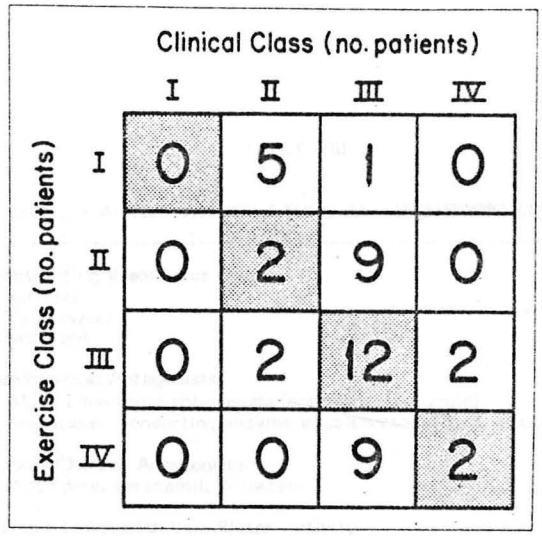
(from Firth et al, 1982)



(from Firth et al, 1982)

Figure 7: The percent change in pulmonary capillary wedge pressure (PCW) versus the percent change in left ventricular end-diastolic volume index (EDVI) in response to nitroprusside infusion. The 95 percent confidence limits of the intercept are shown.

Franciosa (1979) first drew attention to the marked discrepancy that may exist between a patient's subjective assessment of symptomatic status (assessed according to the New York Heart Association criteria) and objective evidence of exercise capacity (Figure 8).



(from Franciosa, 1979)

Figure 8: Comparison of clinical and exercise classification of patients with congestive heart failure. Shaded boxes indicate concordance.

An objective assessment of exercise capacity, by bicycle or treadmill exercise testing, is invaluable in determining the chronic efficacy of a cardiotonic agent. Ideally, oxygen consumption and the anaerobic threshold should be measured during this procedure (Weber et al, 1982a), but few laboratories are equipped to perform these evaluations on a routine basis. Unfortunately, a large percentage of patients with congestive heart failure are unable to perform a meaningful exercise test. It is also clear that an improvement in hemodynamics (particularly acutely) may not necessarily translate into an improvement in exercise capacity.

C. **Orally Active Vasodilator and Inotropic Drugs:**

A great deal of enthusiasm surrounded the initial use of vasodilators in the management of congestive heart failure. Reducing the load on the dysfunctioning myocardium seemed a conceptually attractive way of improving pump performance, particularly when the compensatory vasoconstriction appeared to be excessive. During the past two years, the cardiological literature has been replete with publications on this subject. Many of the studies have been poorly controlled and anecdotal. In reviewing the present status of these agents, I shall confine myself whenever possible to studies that use objective end-points and a controlled study design. A recent review by Milton Packer (1983) provides an excellent summary of the present status of orally active vasodilator and inotropic drugs (Table VIII).

TABLE VIII

ORALLY ACTIVE VASODILATORY AND INOTROPIC DRUGS

Direct-acting Vasodilator Drugs
Nitrates
Hydralazine
Minoxidil

Neurohumoral Antagonists
Alpha-adrenergic antagonists (prazosin, trimazosin)
Angiotensin converting enzyme inhibitors (captopril, enalapril)

Calcium Channel Antagonists
Nifedipine, verapamil, diltiazem

Inotropic Drugs With Vasodilator Activity
Beta-agonist agents (prenalterol, pirbuterol, salbutamol, terbutaline)

Noncatecholamine Nonglycoside Inotropic Drugs
Amrinone, milrinone
MDL 17043, MDL 19205

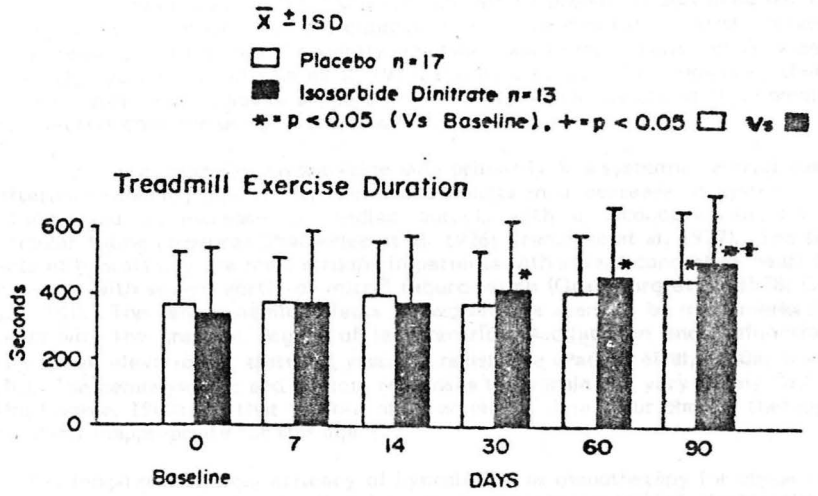
Cardiac Glycosides

(after Packer, 1983)

1. Nitrates: Sublingual nitroglycerin was the first vasodilator to be used in the management of congestive heart failure (Johnson et al, 1957). More recently, isosorbide dinitrate, a long-acting oral preparation has been the preferred agent and the majority of the current literature relates to experience with this agent. The use of transdermal nitrate preparations is currently under investigation.

Nitrates act directly on venous capacitance vessels to produce a reduction in right and left-sided filling pressures, i.e., a predominant preload reducing effect (Franciosa et al; 1974: Gray et al, 1975). In larger dosages (40 to 100 mg orally or with high-dose intravenous nitroglycerin), nitrates also reduce afterload and may produce an increase in cardiac output, particularly in patients with a very low cardiac index (Franciosa et al, 1978a) or aortic or mitral regurgitation (Sniderman et al, 1974).

The beneficial hemodynamic effects of nitrates appear to translate into an improvement in exercise capacity during long-term administration (Franciosa and Cohn, 1979a; Franciosa et al, 1980). *These uncontrolled observations have been confirmed by two randomized double-blind, placebo-controlled studies of isosorbide dinitrate 160 mg orally daily for 3 months* (Franciosa et al, 1978b; Leier et al, 1983). This is illustrated in Figure 9.



(from Leier et al, 1983)

Figure 9: Exercise capacity determined by outpatient treadmill testing at specific intervals. Chronic isosorbide dinitrate administration results in significant improvement in exercise capacity versus placebo.

Nitrates are generally well tolerated and are inexpensive. Headaches, flushing and dizziness occur infrequently with these agents in patients with congestive heart failure. Tolerance may develop to the hemodynamic effects of nitrates particularly with transdermal preparations with long-term administration (Olivari et al, 1983). This seems to affect the systemic arterial bed much more than the venous bed (Leier et al, 1983) so that the beneficial effects on cardiac output may be lost. However, this does not seem to be important since an improvement in exercise capacity occurs despite the absence of an increase in cardiac output. Maximal oxygen consumption is enhanced during long-term treatment. This may be due to the training effect of repeated more comfortable submaximal exercise with reduced pulmonary capillary pressures (Franciosa et al, 1980). This training effect is well-illustrated in Figure 10. However, repeated exercise testing per se also seems to have a training effect since the exercise capacity of the placebo group also increases, but to a lesser degree.

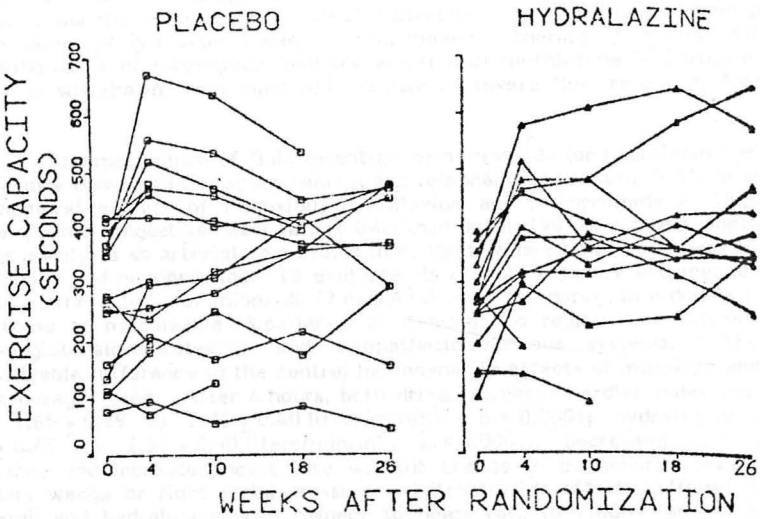
Although chronic nitrate therapy appears to produce a sustained hemodynamic and symptomatic improvement, the clinical benefits are generally modest (Packer, 1983). For this reason, nitrates are frequently combined with other orally active vasodilators, particularly hydralazine (Massie et al, 1977; Pierpont et al, 1978). However, there are at present no controlled studies to support the contention that the use of this combination is more effective than the use of nitrates alone.

2. Hydralazine: Hydralazine acts primarily as a systemic arterial vasodilator, or afterload reducing agent. It, therefore, results in a decrease in systemic vascular resistance and an increase in cardiac output, with a secondary reduction in left ventricular filling pressure (Chatterjee et al, 1976; Franciosa et al, 1977). The beneficial effects of hydralazine are most striking in patients with severe congestive heart failure in conjunction with severe aortic or mitral regurgitation (Greenberg et al, 1978; Greenberg et al, 1980). The hemodynamic effects of hydralazine seem to be most marked in those patients with the greatest degree of left ventricular dilatation and dysfunction and/or most marked elevation of systemic vascular resistance (Packer et al, 1980a; Wilson et al, 1983b). The hemodynamic and clinical responses to hydralazine vary widely (Wilson et al, 1983b; Packer, 1980b) so that the use of an empirical dosage for chronic therapy may be particularly inappropriate for this agent.

The long-term clinical efficacy of hydralazine as monotherapy for congestive heart failure is very much in doubt. ***Two long-term, placebo-controlled, double-blind studies have demonstrated no improvement in exercise capacity versus placebo*** (Franciosa et al, 1982; Weber et al, 1981a). In the larger of these two studies, hydralazine 200 mg daily was administered for 6 months (Franciosa et al, 1982). The effects of hydralazine and placebo, respectively, on exercise capacity in this study are shown in Figure 10.

In contradistinction, uncontrolled studies suggest that when hydralazine is combined with nitrates, symptomatic improvement ensues (Massie et al, 1981; Franciosa and Cohn, 1979b). The Veterans Administration is currently conducting a long-term multicenter study of the chronic effects of prazosin or hydralazine-isosorbide dinitrate versus placebo in patients with congestive heart failure in an attempt to resolve the question of efficacy of both these forms of therapy.

There are several problems with the use of hydralazine in congestive heart failure. First, the dosage requirements are highly variable. This makes it almost mandatory to perform invasive hemodynamic monitoring to ensure that an effective dose is administered (Packer et al, 1980b). Second, tolerance inexplicably occurs in 20 to 30 percent of patients with chronic administration (Packer, 1983). Third, adverse reactions may occur. These may be minor, e.g., headaches, palpitations or flushing, or more severe, e.g., nausea and vomiting, necessitating withdrawal of the drug. Myocardial ischemia and infarction may occur during initiation of therapy (Packer et al, 1981). Systemic lupus erythematosus may occur with high dosage given for a protracted period (Alarcon-Segovia et al, 1967). Fluid retention may also be troublesome and necessitate an increase in diuretic therapy (Markham et al, 1983a). This may be particularly troublesome in patients who are already on large doses of diuretics.



(from Franciosa et al, 1983)

Figure 10: Effects of long-term hydralazine administration on exercise capacity in patients with chronic congestive heart failure. Control values (week 0) represent the average of two tests done 2 weeks apart. No differences between groups are significant at any time.

3. Minoxidil: Minoxidil is a direct-acting systemic arterial vasodilator with similar hemodynamic effects to hydralazine (Franciosa and Cohn, 1981; McKay et al, 1982; Markham et al, 1983a). Two uncontrolled studies demonstrated an improvement in exercise capacity and maximal exercise oxygen consumption (Nathan et al, 1982) or in hemodynamics and symptomatic status (McKay et al, 1982) when fluid retention could be controlled. These results await objective confirmation. Packer has suggested that the dosage requirements of minoxidil may be more uniform than with hydralazine and some patients who become tolerant to hydralazine may still respond to minoxidil (Packer et al, 1983).

A side-effect peculiar to minoxidil is hirsutism, which may be extremely troublesome in female patients. Systemic arterial hypotension, reflex tachycardia and myocardial ischemia might also be anticipated but do not seem to have been major

problems in patients with congestive heart failure. Clearly, *the major side effect limiting the usefulness of this agent is its marked propensity to cause fluid retention that may be resistant to diuretic therapy* (McKay et al, 1982; Nathan et al, 1982; Markham et al, 1983a). In our own experience, 6 out of 7 patients with NYHA Class IV congestive heart failure gained weight after 1 week of oral minoxidil therapy (31 ± 9 mg daily). Despite increasing doses of furosemide (and the addition of metolazone in 1 patient), 2 patients had to be withdrawn from minoxidil because of severe fluid retention (Markham et al, 1983a).

The mechanism of fluid retention with minoxidil (or hydralazine) is not certain. We recently compared the acute central and regional hemodynamic effects as well as the neurohumoral effects of minoxidil, hydralazine and nitroprusside in 15 patients with severe chronic congestive heart failure (Markham et al, 1983a). To test whether minoxidil acts primarily as an arterial vasodilator in congestive heart failure, it was compared with hydralazine and nitroprusside. To evaluate its chronic efficacy and mechanism of fluid retention, the effects of minoxidil (7 patients) were compared, in a double-blind manner, with those of hydralazine (8 patients) on central and regional hemodynamics and the renin-angiotensin-aldosterone and sympathetic nervous systems. There was no demonstrable difference in the central hemodynamic effects of minoxidil and hydralazine in the dosages used. After 6 hours, both drugs increased cardiac index (minoxidil group from 1.65 ± 0.29 to 2.26 ± 0.40 liters/min/m^2, $p < 0.0001$; hydralazine group, from 1.88 ± 0.61 to 2.34 ± 0.90 liters/min/m^2, $p < 0.0001$), decreased systemic vascular resistance and increased heart rate without change in pulmonary arterial, pulmonary capillary wedge or right atrial pressures. Nitroprusside effects differed from those of minoxidil and hydralazine with respect to heart rate ($p < 0.005$) and mean pulmonary arterial ($p < 0.007$) and right atrial ($p < 0.009$) pressures. Nitroprusside also decreased relative hepatomesenteric flow compared with the other two agents ($p < 0.005$). Neither renal blood flow, glomerular filtration rate, filtration fraction, nor urinary sodium excretion were significantly altered acutely by any of the three drugs (Table IX).

TABLE IX

MEASUREMENTS OF RENAL FUNCTION: BASELINE VERSUS 6 HOURS OF THERAPY

	Baseline	Nitroprusside*	Baseline	Minoxidil	Baseline	Hydralazine
Inulin clearance (ml/min)	52 ± 32	61 ± 29	89 ± 51	78 ± 33	50 ± 28	58 ± 28
Filtration fraction	0.22 ± 0.09	0.22 ± 0.10	0.26 ± 0.08	0.28 ± 0.21	0.25 ± 0.12	0.25 ± 0.14
Urinary sodium excretion (μEq/min)	8.2 ± 10.7	5.2 ± 6.1	4.9 ± 9.8	1.5 ± 1.7	4.6 ± 6.3	5.3 ± 7.0

*60 minutes of nitroprusside infusion at a constant dosage.

(from Markham et al, 1983a)

Minoxidil and hydralazine did not differ in their neurohumoral effects: both agents produced an increase in plasma norepinephrine concentration ($p < 0.003$) and plasma renin activity ($p < 0.04$) after one week of therapy, but no change in plasma epinephrine or aldosterone concentrations. After 1 week of double-blind therapy, fluid retention was a greater problem with minoxidil than with hydralazine. Thus minoxidil behaves primarily as an arterial vasodilator in congestive heart failure, fluid retention is a severe adverse effect, and the greater degree of fluid retention with minoxidil than hydralazine is not attributable to differing acute effects on total renal blood flow or function, or differing effects on the renin-angiotensin-aldosterone or sympathetic nervous systems. A mechanism that could not be addressed by our study is an intrarenal redisribution of blood flow away from the outer renal cortex, such as that which occurs with minoxidil administration in normotensive dogs (Zins, 1974). This possibility merits further investigation.

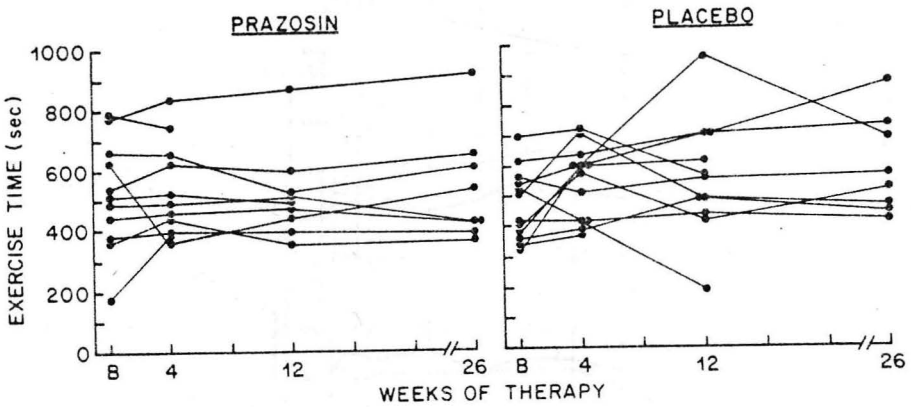
4. Alpha-Adrenergic Blocking Agents:

4a. **Prazosin.** Prazosin produces vasodilatation by selective post-synaptic alpha-adrenergic sympathetic blockade (Graham and Pettinger, 1979). It has been shown to produce a balanced effect on both the venous and arterial systems, with a resultant increase in cardiac output and decrease in pulmonary congestion in patients with congestive heart failure (Awan et al, 1978a,b). However, its long-term efficacy is in dispute, and tolerance appears to be a common problem (Packer et al, 1979; Arnold et al, 1979; Elkayam et al, 1979; Desch et al, 1979).

Several double-blind, placebo-controlled studies have attempted to define the chronic efficacy of prazosin therapy in congestive heart failure. In 16 patients, Colucci et al (1980a; 1981a) demonstrated an improvement in both left and right ventricular function (by radionuclide ventriculography) and an increase in exercise tolerance versus placebo after 2 months of therapy with prazosin 20 mg daily. Harper et al (1980), in a double-blind, placebo-controlled, cross-over study demonstrated acute hemodynamic benefit from prazosin but a marked attenuation of these hemodynamic effects and no improvement in exercise capacity after 1 month of oral therapy. Higginbotham et al (1983) performed a 6-month, double-blind, placebo-controlled study of prazosin in 22 patients with chronic congestive heart failure and demonstrated no improvement in exercise tolerance (despite a slight improvement in radionuclide-determined variables) attributable to prazosin. We also recently completed a placebo-controlled, double-blind, randomized study in 25 patients lasting 6 months and demonstrated no improvement in either radionuclide-determined variables (left ventricular volumes and ejection fractions at rest and during exercise, right ventricular ejection fraction at rest), exercise time or exercise workload in response to prazosin at any time (Markham et al, 1983b). The effects of prazosin on total exercise time in our study are shown in Figure 11.

The development of hemodynamic tolerance and the resultant loss of clinical benefit appears to be a major factor limiting the usefulness of prazosin for chronic therapy of congestive heart failure. Some investigators have suggested that tolerance is not a major problem and may resolve spontaneously or be overcome by an increase in dosage of prazosin (Awan et al, 1981a), but this is not the general experience. It has been suggested that tolerance may be due to the activation of counterposing neurohumoral forces (the sympathetic nervous system or renin-angiotensin system) (Colucci et al, 1980b and 1981b; Stein et al, 1981). In our experience, any increase in

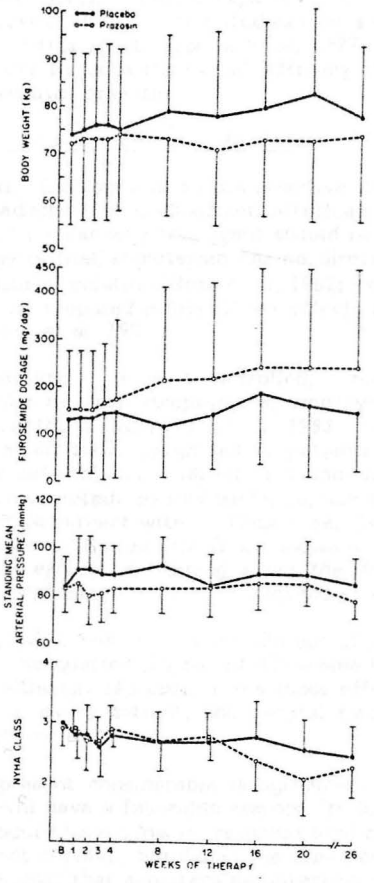
plasma renin activity or plasma norepinephrine that occurred was not sustained and, therefore, seems an unlikely explanation for the observed tolerance (Markham et al, 1983b). Likewise, the observation that tolerance can be reversed by the administration of spironolactone (Rouleaux et al, 1981) has not been confirmed (Packer, 1983).



(from Markham et al, 1983b)

Figure 11: Total exercise time in the prazosin and placebo-treated patients. Each line represents the data from one patient. There was no significant difference in response between the two groups.

Prazosin is well tolerated and has very few side-effects apart from postural hypotension with administration of the first dose in 3 to 5 percent of patients (the so-called first-dose phenomenon) (Graham et al, 1976). With chronic administration, neither postural hypotension nor fluid retention presents a significant problem (Figure 12).



(from Markham et al, 1983b)

Figure 12: Weight, furosemide dosage, standing mean arterial blood pressure, and NYHA class over the 6-month study period. Data are presented as the mean $\pm$ standard deviation for the prazosin group (open circles) and placebo group (solid circles), respectively. Weight increased significantly with time in both groups ($p < 0.0001$). The other variables did not change significantly.

4b. **Trimazosin.** Trimazosin is an analog of prazosin that also produces a "balanced" effect on the venous and arterial beds in patients with severe congestive heart failure, presumably due to post-synaptic, alpha-adrenergic blockade (Franciosa and Cohn, 1978; Awan et al, 1979). The overall clinical experience with trimazosin is very much more limited than with prazosin. However, two studies have suggested a beneficial effect with chronic administration of this agent (Aronow et al, 1977; Weber et al, 1980). There are at present insufficient data to judge the overall efficacy of trimazosin or to establish whether it has any advantages over prazosin.

5. Angiotensin Converting Enzyme Inhibitors:

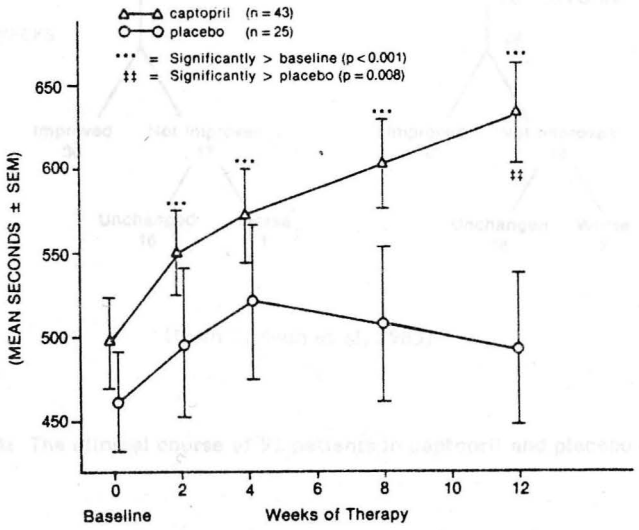
5a. **Captopril.** Captopril is an orally-active converting enzyme inhibitor that produces a balanced reduction of preload and afterload (Tarazi et al, 1979; Davis et al, 1979). It is not entirely clear why this agent should reduce filling pressures since experimental evidence suggests that angiotensin has no direct effect on the pulmonary vasculature or the limb venous circulation (Rose et al, 1962; DePasquale and Burch, 1963). One explanation that has been proposed is that these effects are due to an alteration in ventricular compliance (Packer et al, 1983).

Two double-blind, placebo-controlled, randomized studies have demonstrated both hemodynamic and symptomatic improvement after 3 months of continuous therapy with captopril (Kramer et al, 1983; Cannon et al, 1983). The multicenter study (Cannon et al, 1983) comprised 91 patients (49 captopril, 42 placebo) and is the largest randomized clinical trial of a vasodilator drug in patients with congestive heart failure yet completed. In this study, captopril produced a mean increase in exercise tolerance time of 24 percent with continued use. The results of serial exercise tests in the captopril and placebo-treated groups are shown in Figure 13. *This figure also demonstrates very clearly the effects of training during the first 4 weeks in the placebo-treated group and serves to emphasize the need for placebo-controlled evaluations.*

In this study, two-thirds of patients (30 out of 49) appeared to improve in response to captopril while one-quarter (10 out of 42) seemed to improve in response to placebo (Figure 14). Thus, although captopril is the most effective vasodilator in heart failure, it is not effective in every patient, and general supportive measures may also result in symptomatic improvement.

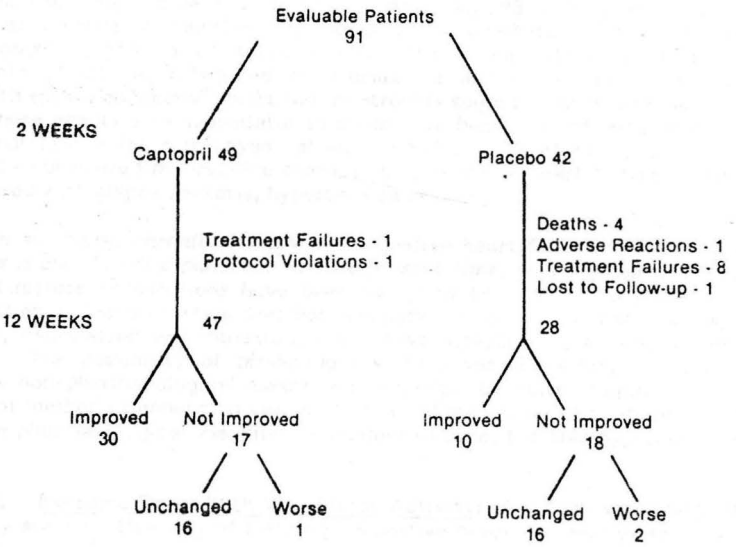
There is at present considerable disagreement as to the best method of determining which patients will have a favorable response to long-term captopril therapy. Whether the absence of an acute hemodynamic response implies that long-term therapy is unlikely to be beneficial is not certain. Similarly, the presence of elevated plasma renin activity would intuitively suggest that angiotensin-converting enzyme inhibition might be therapeutically effective, but some patients without an elevation in plasma renin activity (or reduced serum sodium) also show a beneficial response to long-term therapy. Therefore, long-term captopril therapy remains somewhat empiric. Although both long-term, double-blind studies of captopril (Kramer et al, 1983; Cannon et al, 1983) used 100 mg three times daily, there is theoretical support for use of a much smaller dosage, e.g., 25 to 50 mg, t.i.d. (Romankiewicz et al, 1983).

The major side-effect limiting the use of captopril is the development of systemic arterial hypotension. Therefore, patients with the lowest initial blood pressure are at greatest risk. The hypotensive effects of captopril can be minimized by the use of very small initial dosages (e.g., 6.25 mg) and by reducing diuretic usage. Indeed, *a particular advantage of captopril is that, unlike most other vasodilators, it does not aggravate fluid retention and frequently enables one to reduce the diuretic dosage.* A pruritic, erythematous, maculopapular rash occurs in 5 to 8 percent of patients and is the most common adverse reaction that necessitates discontinuation of therapy. An increase in blood urea nitrogen occurs in about 20 percent of patients which usually responds to a reduction in diuretic dosage or a decrease in captopril dosage. Neutropenia and proteinuria are serious concerns but occur infrequently in patients with congestive heart failure (Romankiewicz et al, 1983).



(from Cannon et al, 1983)

Figure 13: Comparison of exercise tolerance times for cohorts of patients treated with captopril or placebo. Data are expressed as mean ± standard error of the mean.



(from Cannon et al, 1983)

Figure 14: The clinical course of 91 patients in captopril and placebo groups.

5b. **Enalapril.** A number of other angiotensin-converting enzyme inhibitors are currently being studied (Cushman et al, 1982). Enalapril is the analog that has been most thoroughly investigated (Gavras et al, 1978; DiCarlo et al, 1983; Fitzpatrick et al, 1983). It has a longer duration of action, and does not possess a sulfhydryl group, which has been held responsible for some of the idiosyncratic adverse effects of captopril (Vlasses et al, 1981). It appears to produce similar hemodynamic and clinical benefits to captopril in patients with severe congestive heart failure. It remains to be seen whether it will prove as effective as captopril with a lower incidence of side-effects.

6. Calcium-Channel Antagonists: The calcium-channel antagonists, verapamil, nifedipine and diltiazem, all possess vasodilator activity and so might prove useful in the management of congestive heart failure. However, unlike the other vasodilators discussed, they also have *negative inotropic* effects. Of the three, nifedipine produces the most vasodilatation, which generally more than offsets its negative inotropic effects in patients with well-preserved ventricular function and results in an increase in cardiac output; however, in those with depressed ventricular function, the response is unpredictable (Matsumoto et al, 1980; Klugmann et al, 1980; Brooks et al, 1980; Ludbrook et al, 1982). The same is true of verapamil (Chew et al, 1981), and presumably diltiazem. Worsening of ventricular function may occur and exacerbate heart failure due to the negative inotropic effects of these drugs. Preliminary data which compare the hemodynamic effects of nifedipine to hydralazine and nitroprusside, respectively, in patients with severe congestive heart failure strongly suggest that nifedipine is inferior to either of these agents as a vasodilator in congestive heart failure because of its marked negative inotropic effects (Elkayam et al, 1983a,b). Therefore, calcium antagonists should not be considered as first-line therapy for congestive heart failure unless it is mild and associated with angina pectoris, hypertension or both.

In summary, chronic therapy of congestive heart failure with pharmacological vasodilators is clearly not a panacea. At the present time, only captopril, and to a lesser extent oral nitrate preparations have been shown to be superior to placebo in a large group of patients. However, this does not preclude the possibility that other agents, such as prazosin, hydralazine and minoxidil, may prove effective in a minority of selected individuals. The possibility of producing sustained vasodilatation, particularly during exercise, by non-pharmacological means is intriguing. Exercise training is an effective physiological method of enhancing vasodilatation and may prove to be more effective than many of the pharmacological vasodilators studied to date, but this hypothesis remains to be proven.

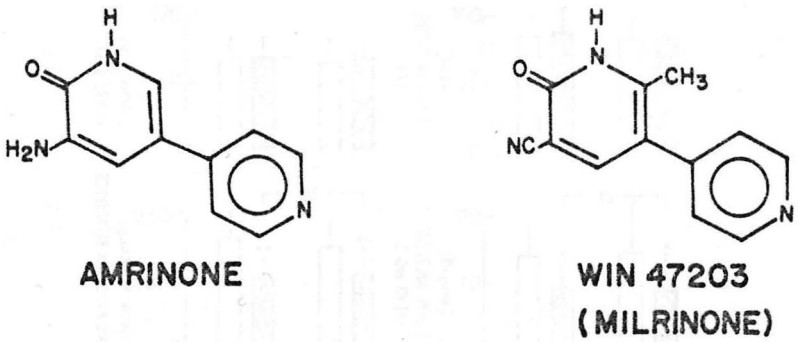
7. Inotropic Drugs With Vasodilator Activity: Although vasodilator therapy is conceptually an attractive way of treating congestive heart failure, systemic hypotension may preclude its use, and necessitate therapy with a positive inotropic agent. In the intensive care unit, **dopamine** and **dobutamine** by intravenous administration have supplanted the use of digitalis for this purpose. Both agents are sympathomimetic amines and are considerably more powerful than the cardiac glycosides with fewer side effects (Goldstein et al, 1980). In addition to its positive inotropic effects, dobutamine is a vasodilator while dopamine is a vasoconstrictor (with the exception of the renal vascular bed where flow is increased) (Loeb et al, 1971; Stoner et al, 1977; Leier et al, 1978; Sonnenblick et al, 1979). The use of these agents individually, or in combination may be very efficacious (Richard et al, 1983). The disadvantages with these agents are, first, that they depend on an already depleted myocardial norepinephrine store for their action (and further deplete this store) with a resulting decline in efficacy over 48 to 72 hours, (Unverferth et al, 1980) and second, that they are not active orally.

7a. **Orally Active Sympathomimetic Amines.** A number of orally-active sympathomimetic amines have recently been synthesized for use in heart failure. These agents include **prenalterol** (Awan et al, 1981b, Kirlin et al, 1981), **pirbuterol** (Awan et al, 1983; Sharma et al, 1981), **salbutamol** (Sharma and Goodwin, 1978), and **terbutaline** (Slutsky, 1981). These agents possess both positive inotropic ($\beta 1$) and vasodilator ($\beta 2$) effects in varying degrees, and the extent to which the increase in cardiac output produced by each of these agents is due to an increase in contractility versus a decrease in afterload is in dispute (Tweddel et al, 1982).

These sympathomimetic agents all produce an increase in cardiac output and a decrease in pulmonary capillary wedge pressure, both at rest and during exercise, when given acutely to patients with congestive heart failure. The most promising of these agents for long-term use appeared to be pirbuterol. However, it was found to produce no improvement in exercise capacity with chronic use, significant adverse reactions (palpitations, tremulousness, tachycardia), exacerbation of angina pectoris and an increase in ventricular arrhythmias (Colucci et al, 1981c ; Weber et al, 1982b). In addition, rapid hemodynamic tolerance to its effects were reported (Colucci et al, 1981d). For all these reasons, clinical investigation of this agent was terminated by the Food and Drug Administration. The mechanism of tolerance to pirbuterol may relate to down-regulation of beta-adrenergic receptors (Colucci et al, 1981d). If this in indeed the case, it augurs badly for other sympathomimetic amines that may be subject to similar problems and/or depend on the presence of endogenous catecholamine stores for their action.

7b. **Non-Catechol, Non-Glycoside Inotropic Agents:** Recently, a group of drugs (amrinone, milrinone, MDL 17043 and MDL 19205), which are non-catecholamine, non-glycoside inotropic agents have been investigated in patients with congestive heart failure. Although these agents inhibit phosphodiesterase, leading to an accumulation of intracellular cyclic AMP, the precise mechanism whereby they increase contractility is a matter of controversy. In addition, these agents are powerful vasodilators.

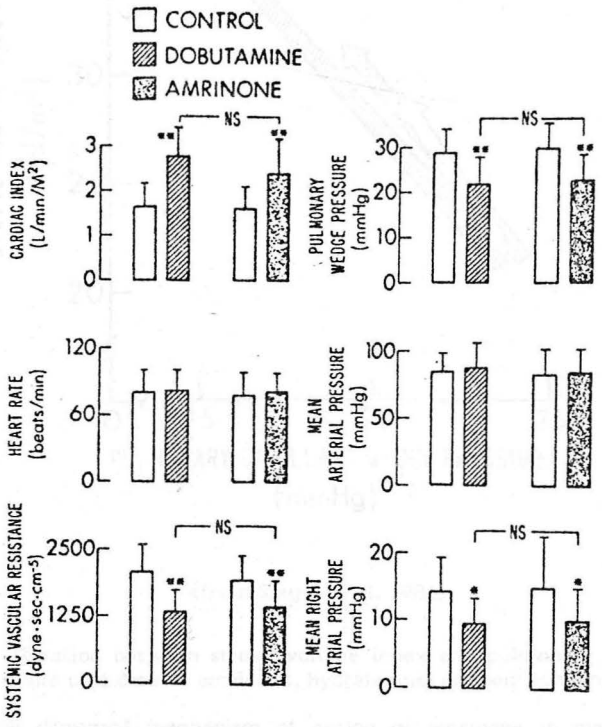
Amrinone and milrinone are bypyridine nucleotides that are structurally similar (Figure 15).



(from Baim et al, 1983)

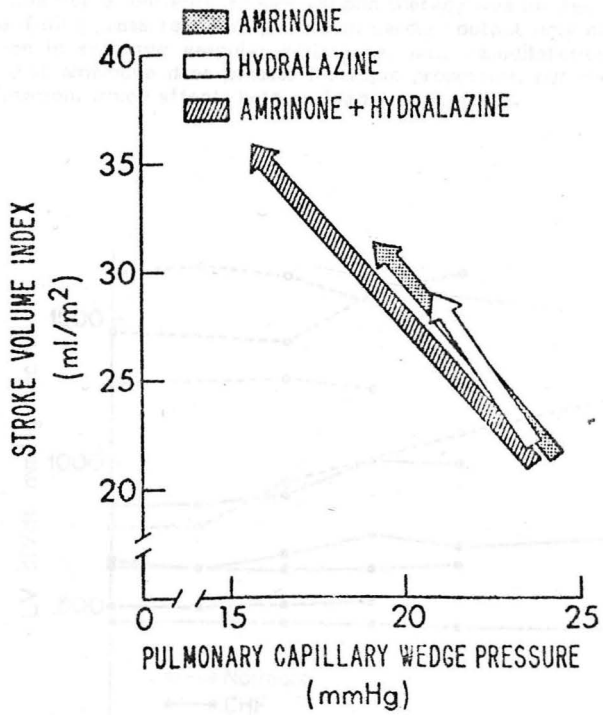
Figure 15: Chemical structures of amrinone and milrinone (WIN 47203), the 2-methyl, 5-carbonitrile derivative.

Most of the clinical experience has been with **amrinone.** When administered either intravenously or orally, it produces marked hemodynamic benefit in most patients with severe congestive heart failure (Benotti et al, 1978; LeJemtel et al, 1979; LeJemtel et al, 1980). The acute effects of amrinone appear to be similar to those of dobutamine (Figure 16) (Klein et al, 1981). In addition, the hemodynamic effects appear to be additive to those of hydralazine, a pure vasodilator (Figure 17) (Siegel et al, 1981). An uncontrolled study has also demonstrated an increase in exercise capacity and maximal oxygen consumption in response to amrinone (Weber et al, 1981b).



(from Klein et al, 1981)

Figure 16: Comparative effects of dobutamine and amrinone on hemodynamic status. The initial responses relative to the control values are shown. There are no differences in the hemodynamic responses to the two drugs compared to the control state. * = $p < 0.01$; ** = $p < 0.001$. Horizontal bars indicate $\pm$ standard deviation.

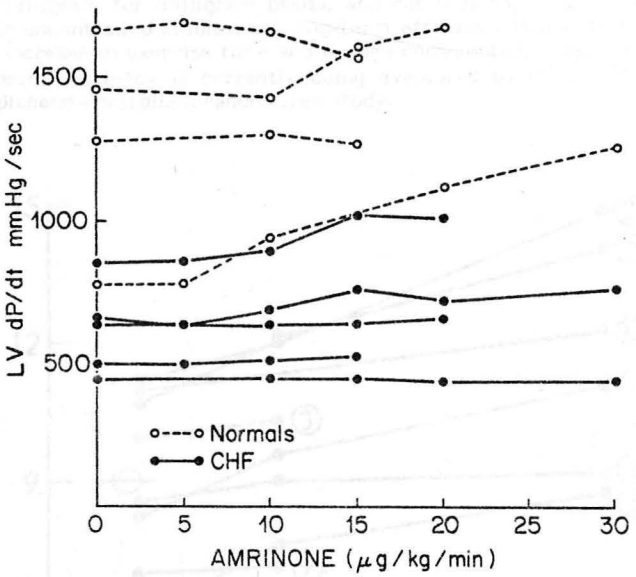


(from Siegel et al, 1981)

Figure 17: Relation between stroke volume index and pulmonary capillary wedge pressure after a single oral dose of amrinone, hydralazine, or their combination.

The dominant mechanism of action of amrinone in man is in dispute (Morgan et al, 1980; Adams et al, 1982; Kondo et al, 1983). Amrinone clearly has a positive inotropic effect in vitro. However, it is difficult to determine in vivo to what extent the increase in cardiac ouput is due to vasodilatation or to an increase in contractility. While some clinical investigators have demonstrated a marked increase in left ventricular dP/dt, (in the face of a decreasing left ventricular end-diastolic pressure and minimal change in heart rate or systemic arterial pressure) (Benotti et al, 1978), which would suggest a marked increase in contractility others have demonstrated very little change in dP/dt (Wilmshurst et al, 1983a).

Our own unpublished observations in 9 patients studied in the cardiac catheterization laboratory suggest that the vasodilator effects are similar while the inotropic effects are rather modest compared to isoproterenol in patients with normal and failing left ventricles (Firth et al, 1984). A significant increase in left ventricular dP/dt occurred in a minority of patients (Figure 18) and therapy was limited by the reduction in left venticular filling pressure. An increase in cardiac output only occurred when there was a reduction in systemic vascular resistance, i.e., vasodilatation. Therefore, our impression is that amrinone does possess inotropic properties, but its major effects are due to vasodilatation, which affects both preload and afterload.

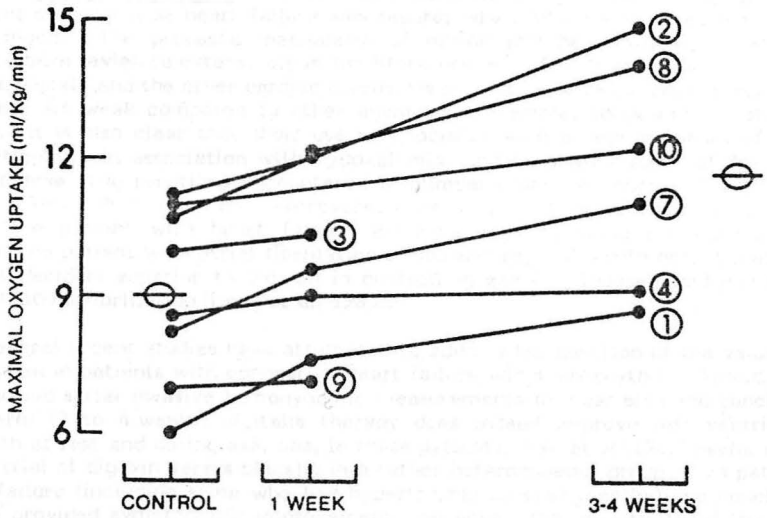


(from Firth et al, 1984)

Figure 18: The effects of incremental dose infusion (20 minute periods) of amrinone in normal individuals and patients with congestive heart failure. These changes occurred in the face of a consistent reduction in left ventricular filling pressure.

The major disadvantages of amrinone relate to its side-effects (Wilmshurst et al, 1983b). Thrombocytopenia (to 50,000 platelets/mm^3) occurs commonly, appears to be dose-related, and resolves on withdrawal of the agent. Gastrointestinal distress occurs in about 30 percent and is the most common reason for discontinuing therapy. Hepatic dysfunction, fever and myalgias occur in 15 to 20 percent. In addition, there is concern that this drug may aggravate or precipitate both ischemia and arrhythmias (Rude et al, 1980). The individual dosage requirements are highly variable so that empiric therapy may be hazardous. The incidence of tolerance to the drug seems to be low. *As with all inotropic agents, there is also the theoretical possibility that long-term administration of this agent may actually hasten the progression of myocardial failure, by depleting energy reserves, and thereby shorten survival* (Katz, 1978).

Milrinone (WIN 47203) appears to have virtually identical hemodynamic effects to those of amrinone. Its major advantages are that it is 20 to 30 times more potent (on a milligram for milligram basis), and has minimal if any side-effects (Baim et al, 1983). In uncontrolled studies, its long-term efficacy has also been reported to be good, with an increase in exercise time and oxygen consumption (Figure 19) (Maskin et al, 1983). Its chronic efficacy is currently being evaluated by means of a multicenter, double-blind, placebo-controlled, randomized study.



(from Maskin et al, 1983)

Figure 19: Changes in maximal oxygen uptake induced by milrinone after 1 and 4 weeks of therapy.

Like amrinone, milrinone does not increase myocardial contractility by inhibiting Na^+-K^+ ATPase or by stimulating cardiac beta-receptors and is effective in the digitalized or norepinephrine depleted heart. However, its precise mode of action is in dispute and to what extent its salutary effects are due to vasodilatation or an increase in contractility remains uncertain (Alousi et al, 1983a,b).

Two other non-catecholamine, non-glycoside, inotropic agents with vasodilator properties, **MDL 17043** and **MDL 19205**, have provoked some interest. MDL 17043 has been studied more completely than MDL 19205, but the available data on both these agents are limited. The acute hemodynamic effects of both agents are similar to those of amrinone and milrinone (Crawford et al, 1983; Uretsky et al, 1983; Petein et al, 1983). Limited long-term follow-up data suggest that MDL 17043 retains its hemodynamic effect and results in symptomatic improvement and an increase in exercise tolerance in most patients (Likoff et al, 1983). However, a number of side-effects, including leucocytosis, hyperglycemia, frequent stools, headache and an increased appetite have been noted. A multicenter double-blind, placebo-controlled study to assess the chronic efficacy of MDL 17043 has just commenced.

Sulmazol (AR-L 115 BS) is yet another non-catecholamine, non-glycoside preparation with positive inotropic and vasodilator properties that is currently in the early stages of clinical evaluation (Thormann et al, 1983).

8. Cardiac Glycosides: For over 200 years, the place of cardiac glycosides in the treatment of congestive heart failure was secure; now this time-hallowed position is being challenged. The proposed mechanism of action and hemodynamic effects of digitalis have been reviewed extensively in the literature (e.g., Smith and Haber, 1973). It is clear that digoxin and the other cardiac glycosides possess positive inotropic properties, although these are weak compared to other agents, for example, dobutamine (Goldstein et al, 1980). It is also clear that their use is associated with a high incidence of side-effects, particularly in association with hypokalemia, and constitute some of the most prevalent adverse drug reactions encountered in clinical practice (Shapiro, 1978; Beller et al, 1971). Although most of the controversy centers around the risk-benefit ratio of digitalis in the patient with heart failure and sinus rhythm, while its place in the treatment of the patient with atrial fibrillation seems secure, it is worth noting that oral verapamil is decidely superior to digoxin in controlling exercise-induced tachycardia in patients with atrial fibrillation (Lang et al, 1983).

Several recent studies have attempted to address the question of the value and need for digoxin in patients with congestive heart failure and sinus rhythm. Arnold et al (1980) performed serial invasive hemodynamic measurements in 9 patients and concluded that long-term (2 to 4 weeks) digitalis therapy does indeed improve left ventricular function, both at rest and during exercise, in these patients. Lee et al (1982) performed a randomized trial of digoxin versus placebo in a rather heterogeneous group of 25 patients with heart failure (including some who had hypertrophic cardiomyopathy) and concluded that digoxin provided symptomatic improvement. However, the objectivity of the end-points used in this study are debatable and no improvement was noted in patients who were already well diuresed. Conversely, Fleg et al (1982) performed a placebo-controlled, cross-over study in 30 patients with congestive heart failure in sinus rhythm and demonstrated no clinical improvement on digoxin and no clinical deterioration on placebo despite small echocardiographic changes suggesting benefit during digoxin therapy. In addition, Gheorghiade and Beller (1983), in a similar group of 25 patients with well-documented congestive heart failure, demonstrated no deterioration in symptomatic status or exercise duration when digoxin was discontinued.

An additional point of concern with cardiac glycosides is that they produce both coronary and systemic *vasoconstriction* (Hamlin et al, 1974; Ross et al, 1960). Conceptually, these effects might be deleterious to the already tenuous myocardial function by increasing the load against which the heart has to eject and decreasing coronary blood flow. However, there is no clinical evidence to suggest that these effects are clinically important with chronic oral digoxin therapy (Firth et al, 1980).

The bulk of the present evidence suggests that chronic oral digoxin therapy results in relatively minor hemodynamic improvement in the patient who has been adequately treated with diuretics. My personal preference, in patients with congestive heart failure and sinus rhythm is to use digitalis sparingly and only when diuretics alone are ineffective. I am particularly concerned about using digitalis in patients with ventricular arrhythmias (particularly if they are already on type I anti-arrhythmic agents), patients with renal dysfunction, or patients who are chronically hypokalemic and/or require massive potassium replacement (Firth, 1982).

It is unclear whether captopril or digoxin should be the next step once diuretics alone are inadequate. This question is currently being addressed by a multicenter, randomized, controlled trial of these two agents in congestive heart failure.

VIII. HEART TRANSPLANTATION AND THE ARTIFICIAL HEART

In end-stage congestive heart failure, good medical therapy is extremely important in improving the patient's symptomatic status but is generally only palliative and is most unlikely to result in a substantial increase in survival. **Heart transplantation,** on the other hand, clearly leads to an increase in survival, as I discussed in an earlier Grand Rounds (Firth, 1981). However, financial and other constraints make this a viable option for only a few hundred people a year world-wide. Suitable candidates must be young (less than 50 years), have no significant pulmonary hypertension, and no other major medical, psychological or social problems. These constraints effectively exclude the majority of patients with end-stage congestive heart failure (approximately 30 to 50,000 per year). The use of an **artificial mechanical heart** seems to offer some promise (Pierce, 1982; deVries, 1983). However, several major problems remain to be resolved. First, the durability of this device is in serious question. After implantation of only a few months, calcification and stress fractures of the polyurethane pumping chambers have occurred and the longest experience in man is only 3 months. Second, an implantable or portable power suply must be developed to enable the patient to ambulate. At the present time, the Jarvik VII artificial heart is powered by large air compressors (approximately the size of a hemodialysis machine) that make physical activity impractical. An artificial heart requires a power supply of 8 to 15 watts (i.e., approximately 1 million times that needed for a cardiac pacemaker). The most feasible option would seem to be lithium-titanium disulfide rechargeable batteries that have 2 to 5 times the energy density of present batteries. These could be worn as a battery pack around the waist and connected via suitable cables to the artificial heart. Third, infection is an ever-present concern, particularly if the artificial heart has to be connected to an external power source. In summary, by the designers' own estimates, it seems most unlikely that the artificial mechanical heart will be a viable option for at least another decade. Even when it is perfected, the mechanical heart is unlikely to have a substantial impact on the population with congestive heart failure because of the expense entailed in this form of therapy.

IX. CONCLUSION

Medical therapy of congestive heart failure has improved markedly over the past few years. The wide variety of agents at out disposal enable us to make most patients

less symptomatic, although the effects on survival may be slight. However, the end-stage heart (like the end-stage kidney, liver or any other organ), from whatever cause, is unlikely to respond dramatically to any therapy apart from replacement. Unfortunately, the resources available to support heart transplantation, even in the wealthiest country in the world, are limited. It therefore seems appropriate that much greater attention should be directed towards the prevention and early detection of cardiac myocyte dysfunction, before systemic decompensation ensues. This implies much greater attention to such antecedents as hypertension and coronary artery disease as well as other treatable causes of cardiac decompensation. It also implies a much more precise understanding of the derangements that occur at a subcellular level in a variety of conditions that culminate in "heart failure." Once the specific derangement is elucidated in a particular condition, it may be possible to direct more specific therapy to the problem that exists rather than to treat the consequences in an empirical manner. In this field, we are just beginning to scratch the surface.

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