Acute Heart Failure Treatment: The Yin and Yang of Therapy

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Eric J. Eichhorn, MD
Associate Professor of Medicine
Division of Cardiology

Eric J. Eichhorn, MD

Associate Professor of Medicine

Division of Cardiology

Interests: I am a clinical cardiologist and an interventional cardiologist with a special interest in chronic heart failure. I have spent the last 12 years examining the effects of ß-adrenergic blockade on myocardial function, energetics, pathological remodeling, morbidity, and mortality in patients with heart failure. I am the Principal Investigator and Co-Chairman for the NHLBI-VA Cooperative Study, the ß-Blocker Evaluation of Survival Trial (BEST). This study is investigating the effects of ß-blockade in patients with advanced heart failure in 90 hospitals in the US and Canada. Current research efforts and collaborators include: 1) the relationship of myocardial viability and response to ß-blockade and the relationship of reverse remodeling to morbidity and mortality (Paul Grayburn, MD, UT Southwestern) 2) the effects of anti-cytokine therapy on ventricular function and remodeling (Doug Mann, MD, Baylor College of Medicine) 3) the effects of endothelin antagonism on ventricular function and morbidity in heart failure. Outside interests of mine include golf, skiing, and SCUBA diving.

The approach to treatment for chronic and acute heart failure are totally different with disparate goals and philosophies. Chronic heart failure is a syndrome of progressive ventricular remodeling (dilatation, fibrosis, cell death and hypertrophy) which is triggered by activation of compensatory neurohormonal pathways (sympathetic nervous system, renin-angiotensin-aldosterone system, endothelins, cytokines)(Figure 1).[1]

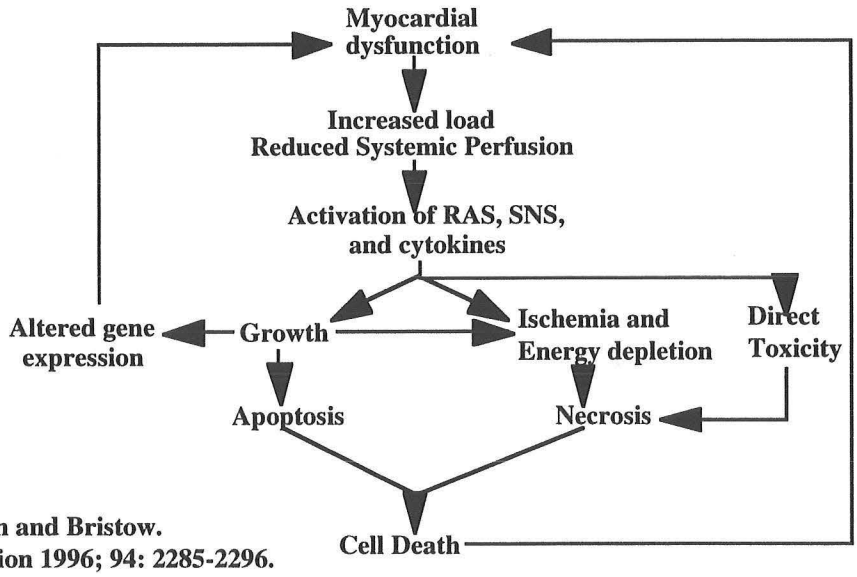


Figure 1

While activation of these neurohormones provide short term compensation (increased contractility and heart rate, sodium and water reabsorption, and vasoconstriction), it may lead to progressive cell death, fibrosis and interstitial remodeling, and a change in gene expression within the myocyte.[1-3] This may lead to further myocardial depression and a vicious cycle is established. Chronic treatments of heart failure which were designed to improve hemodynamics (inotropes, vasodilators), worsened the biology of the myocyte and lead to no long term improvement or in many cases, accelerated death.[4-8] By contrast, chronic treatments which focus on preservation of biological energetics and inhibit intracellular signals for growth by antagonizing neurohormonal activation have lead to improved ventricular function and a slowing or reversal of the pathological remodeling process.[1,9,10] This neurohormonal antagonism is often accomplished at the cost of acutely worsening hemodynamics when initiating therapy.[10-12]

By contrast, the treatment of acute heart failure focuses on hemodynamic improvement and returning the decompensated patient back to compensation. This short term strategy to some degree ignores the long term goals of inhibiting the adrenergic

pathways within the heart (and in fact one strategy for acute heart failure treatment is to stimulate these pathways) and thereby temporarily exposes the patient to some danger of arrhythmias and worsened ischemia (Table 1).

Table 1

	Goals	**Agents Used to Achieve Goals**	**Risk of Initiating Therapy**
Chronic heart failure therapy	To inhibit pathological remodeling (reducing pump failure death) and inhibit stimuli to arrhythmias (to reduce sudden death)	β-blockers (negative inotropes) ACEI (vasodilators)	Hypotension Decompensation Azotemia
Acute heart failure therapy	To improve stroke volume, reduce preload (wedge pressure) to decrease congestion, and/or maintain blood pressure	Vasodilators Inotropes Pressors	↑ arrhythmias ↑ ischemia ↑ hypotension

Yin and Yang- The Yin and Yang of heart failure therapy has to do with the sometimes discrepant goals of acute vs chronic therapy. *Chronic therapy* for CHF is designed to block neurohormonal pathways and improve energetics and biology of myocytes. This is often accomplished as the acute expense of hemodynamics. *Acute therapy* for CHF is designed to improve hemodynamics. This is often accomplished at the expense of energetics and biology of myocytes. Despite the dichotomous goals of acute vs chronic therapy, the ultimate goal of both acute and chronic therapy is to improve the clinical status of the patient and prolong survival.

Identification of the level of decompensation-

In order to properly treat acute decompensation, it is important to not only identify the decompensated patient, but also to identify the level of decompensation. The treatment for acute decompensation is determined by proper identification of the level of decompensation as therapies differ by level. In the chronic heart failure patient, I break this down into 3 levels [12]:

1. Fluid overload responsive to diuretics- most heart failure patients will present with an increase in body weight, increased shortness of breath or edema (lung, legs, abdomen), but no hypotension or organ hypoperfusion. These patients will usually respond to an increase in diuretics.

2. Fluid overload not responsive to diuretics- these patients also have an increase in body weight and edema, but they are either on maximal doses of diuretics, do not respond sufficiently to these doses of diuretics, or have rising BUN/creatinine indicating poor renal perfusion. However, they are not oliguric and do not complain of lightheadedness. More aggressive (IV) diuresis in these patients might throw the patient into renal failure or induce symptomatic hypotension.

3. Incipient cardiogenic shock- these patients have evidence of end-organ hypoperfusion with a rising BUN/creatinine, hypotension, perhaps altered mentation, and even oliguria.

Effects of altered preload and afterload on ventricular function-

Cardiac output in failing and non-failing hearts is determined by multiple different factors including the intrinsic contractility of the myocytes in the chamber, preload, afterload, and heart rate (Figure 2):

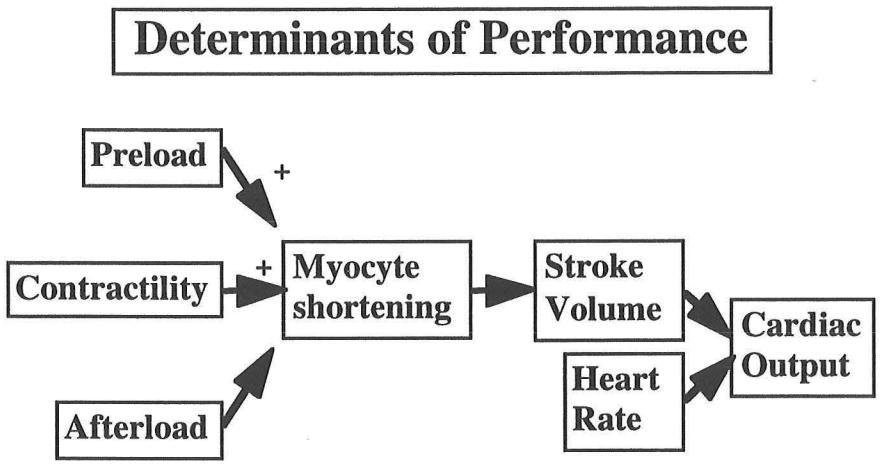


Figure 2

The effect of preload on ventricular function can best be represented by the Frank-Starling relationship (Figure 3).[13] As preload increases, stroke volume increases. Preload can be altered by volume infusion (which increase) or diuretics (which reduce) preload. Failing hearts shift this relationship to the right and downward. Pure inotropic agents shift the relationship upward while arterial vasodilators shift the relationship upwards and to the left. Venodilators shift the relationship to the left and diuretics do not shift the relationship.

Stroke volume is related to afterload (end-systolic wall stress) by the stress shortening relationship (Figure 3).[14] The failing heart shifts this linear relationship

downwards while inotropes shift it upwards. As afterload increases (with pressors), ejection is reduced and as afterload is reduced (with vasodilators), ejection increases.

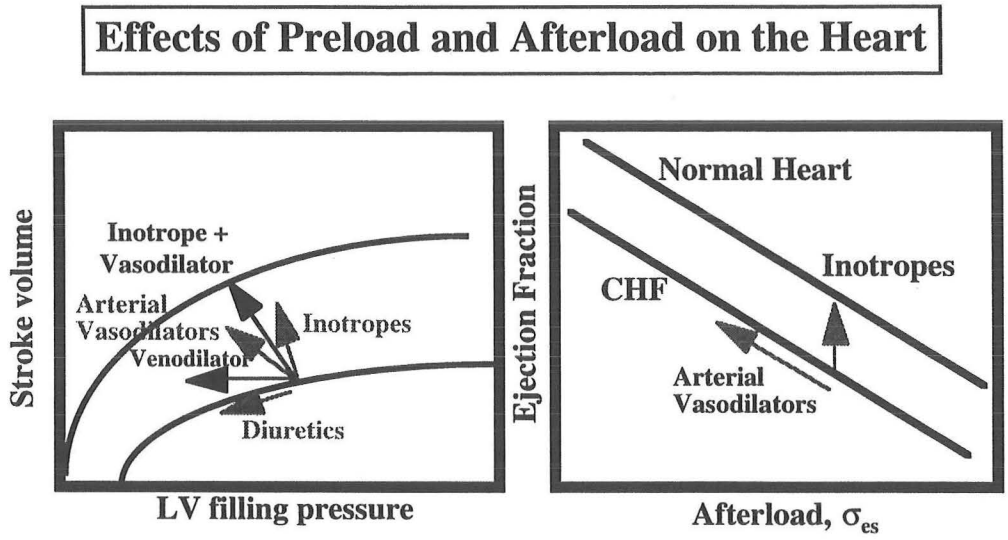


Figure 3

Alternatively, left ventricular systolic and diastolic function can be represented by a pressure-volume loop (Figure 4).[15-18] This loop rotates counter-clockwise beginning at end-diastole and passing through isovolumic contraction, ejection, end-systole, isovolumic relaxation, and filling. The area within the loop is mechanical work. The greater the area subtended by the loop, the greater the mechanical work done by the ventricle.

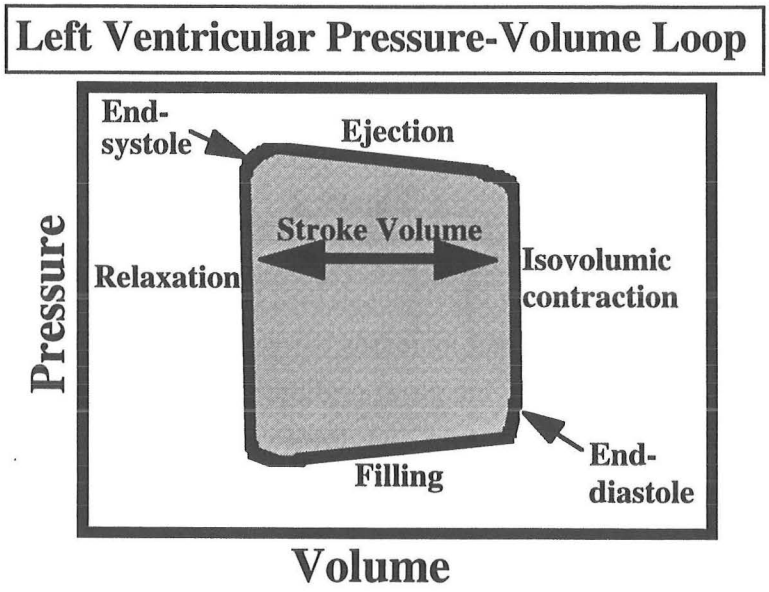


Figure 4

Left ventricular systolic dysfunction will result in a smaller loop with the end-systolic pressure-volume point shifted rightward and downward (Figure 5).[15-17] Changes in chamber stiffness will result in a shift upwards in the diastolic pressure-volume relationship (Figure 5).[18]

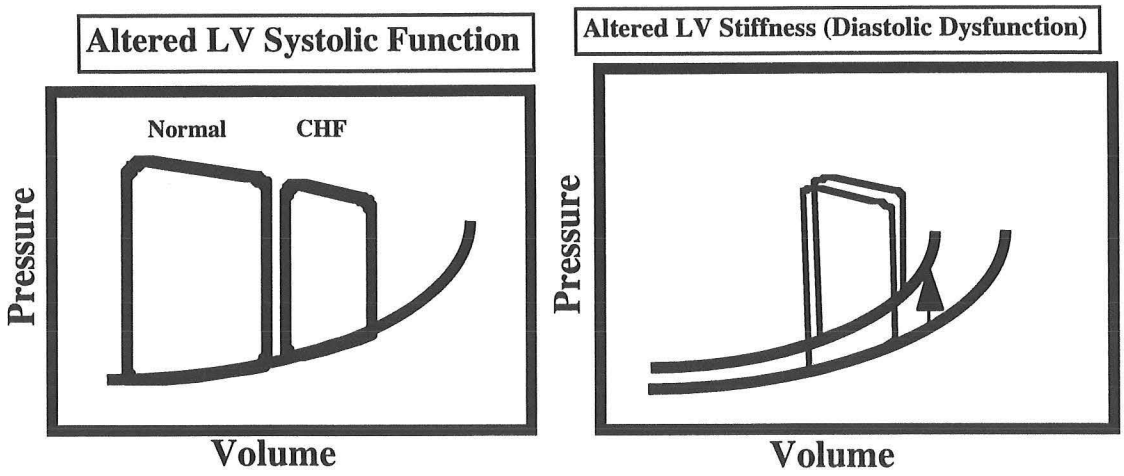


Figure 5

Events which can precipitate acute heart failure-

Acute heart failure can be precipitated by ischemia (including papillary muscle dysfunction resulting in mitral regurgitation or VSD), dietary indiscretion, failure to take medications (diuretics, ACE inhibitors), initiation of ß-blockers, infection, metabolic derangements, and worsening systolic or diastolic function. It is important to understand that heart failure signs and symptoms can develop with either systolic and/or diastolic failure, and both should be treated. Systolic dysfunction may lead primarily to a low stroke volume (low output) while diastolic dysfunction may lead to elevated filling pressures and edema. Most of the time, there is not isolated systolic or diastolic dysfunction.[19] Normally, there is a combination of systolic and diastolic dysfunction.

Treatments for acute heart failure-

There are 3 main categories of treatments for acute heart failure (vasodilators, inotropes, and diuretics) (Table 2). Within each therapeutic type, the drugs differ considerably in their properties. **The object of therapy for acute heart failure is to select an agent or agents which achieve the goal of therapy (reduce preload, improve stroke volume, or increase blood pressure) with the least adverse effect on energetics and arrhythmias.**

Table 2

Agent	Desired Action	Adverse Effect
Diuretics	Reduce preload	↑ azotemia ↑ hypokalemia ↑ hypomagnesemia
Vasodilators	Reduce afterload Reduce preload	↑ azotemia ↑ hypotension
Inotropic agents Digoxin	Increase contractility Reduce SNS activation	Digoxin toxicity ↑ arrhythmias
Non-digoxin inotropes	Increase contractility Increase stroke volume Increase heart rate	↑arrhythmias ↑ ischemia
Pressors	Increase contractility Vasoconstrict Increase heart rate	↑↑↑ arrhythmias ↑↑↑ ischemia

Diuretics- Diuretics reduce preload by inhibiting sodium and water reabsorption in the kidney.[20] However, in states of poor renal perfusion (renal blood flow) due to poor stroke volume, little blood volume is filtered and diuretics become less effective or ineffective. In this situation, improved renal perfusion must be established before diuretics will work. Oral torsemide is more effective than oral furosemide in most cases due to higher bioavailability (80% vs 64%).[21] Thus, in patients with reduced response to furosemide, torsemide can be tried.

Continuous intravenous furosemide is more effective than intermittent bolus furosemide (Figure 6).[22] Continuous furosemide produces a greater urine volume and sodium content than bolus furosemide with less ototoxicity. In addition, combination diuretics which act at different sites in the nephron can be used synergistically [23] Thus, use of metolazone and a loop diuretic can be very effective at diuresis, but may be synergistic at promoting adverse effects of diuretics.

Diuretics are excellent at reducing edema and improving dyspnea. However, they promote hypokalemia and hypomagnesemia as potassium and magnesium are lost in the urine.[24] In addition, as preload is reduced, stroke volume may be reduced by a Starling mechanism (Figure 3) and this may result in worsened renal perfusion (leading to elevated BUN). When monitoring diuretic or vasodilator therapy with pulmonary artery

catheterization, it is important to watch the stroke volume changes as preload changes and not watch cardiac output. As shown in Figure 7, stroke volume can be compromised long before cardiac output begins to fall due to a concomitant increase in heart rate. The increase in heart rate results in an increase in myocardial oxygen consumption which is energetically unfavorable. Finally, these agents activate the renin-angiotensin system [25,26] (Figure 8) which may have adverse consequences both short (vasoconstriction, sodium and water retention) and long term (pathological remodeling, hypertrophy, fibrosis).

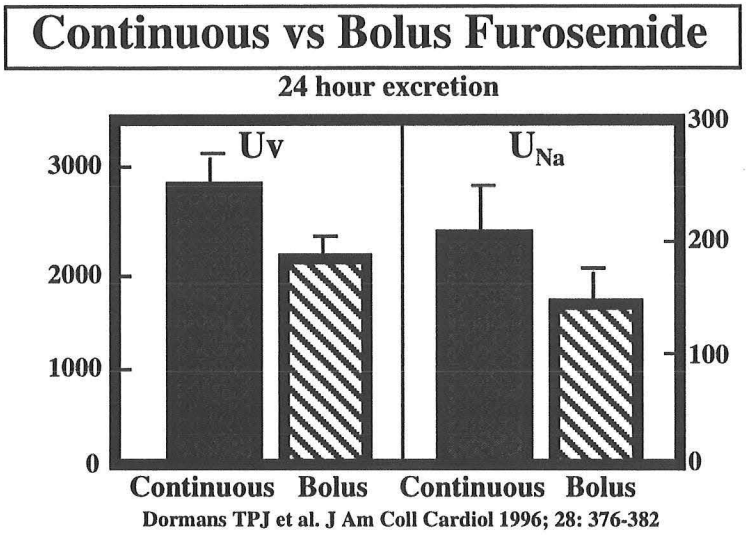


Figure 6

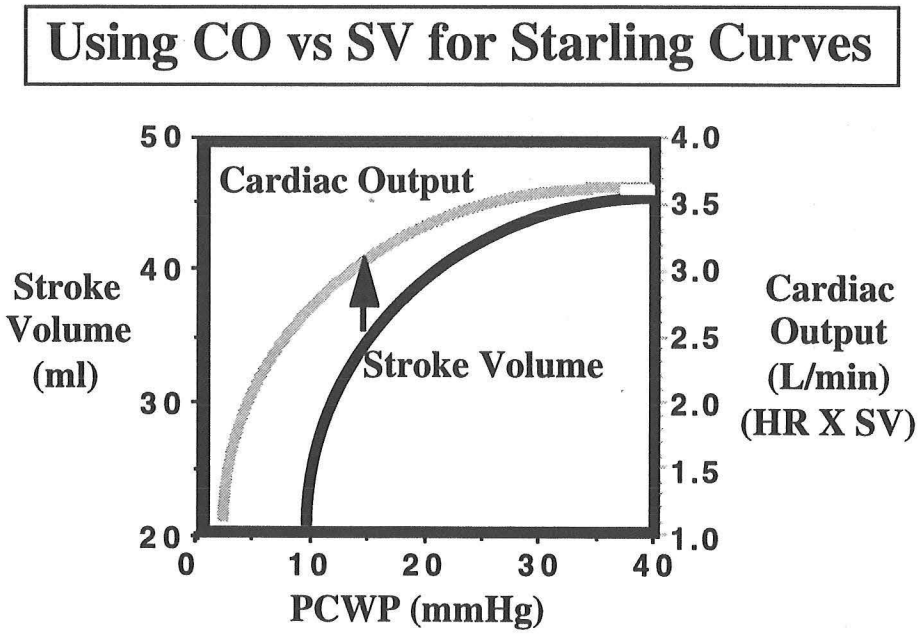


Figure 7

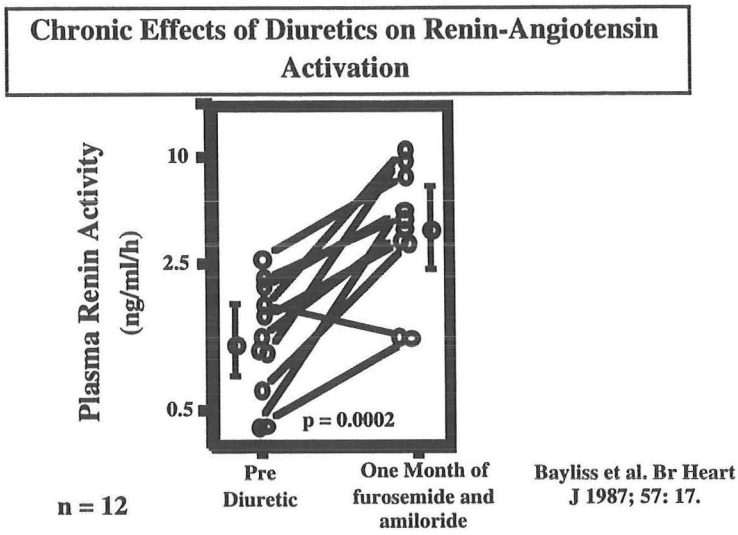


Figure 8

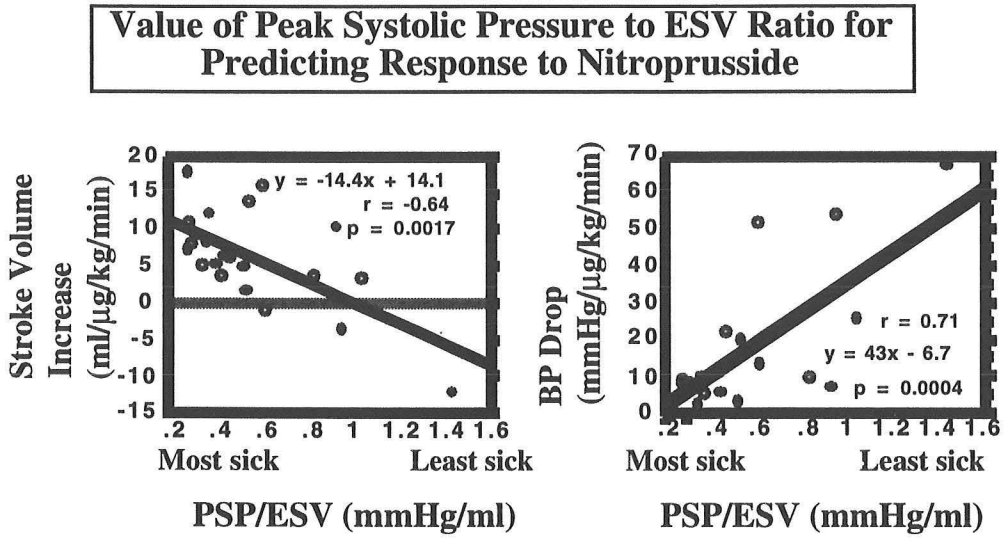
Vasodilators- There are two types of vasodilators, those that primarily affect the arterial system (hydralazine) and those that affect the venous system (nitrates). Some vasodilators are balanced and affect both the arterial and venous system (nitroprusside).

The benefit of vasodilators are: 1) a reduction in load (afterload and/or preload) producing a reduction in wall stress allowing a more complete ejection (larger stroke volume) [27] 2) Reduced wall stress leads to a reduction in myocardial oxygen consumption (energetically favorable) [28,29] 3) Improved oxygen delivery (reduced ischemia) 4) Reduction in afterload also leads to improved relaxation [19] which may lead to a reduction in filling pressures [30] 5) Reduction wall stress may lead to a reduction in neurohormonal activation (reducing arrhythmias) 6) Reduction in wall stress may lead to less tension on the chordae and more coaptation of mitral leaflets leading to less mitral regurgitation.[31]

The choice of vasodilator agents depends on the goal of therapy. If the goal of therapy is a reduction in preload, a venodilator (such as nitrates) would be preferred. If, however, the goal of therapy is to improve forward output, an arterial or mixed action vasodilator would be better (ACE inhibitor or nitroprusside). If both a reduction in preload and afterload is needed to improve stroke volume while reducing wedge pressure, nitroprusside would be the agent of choice.

Many physicians fear using nitroprusside because of hypotension. However, many patients with heart failure have a high systemic vascular resistance. As this is reduced with nitroprusside, the fall in SVR is offset by an increase in stroke volume which leads to a maintenance of systolic blood pressure. A study by Heesch and Eichhorn demonstrated that patients with the largest end-systolic volume or the lowest ratio of peak systolic pressure to

end-systolic volume (i.e. the sickest patients) had the smallest reduction in blood pressure per dose of nitroprusside (Figure 9).[27] Conversely, the patients with the lowest blood pressure or lowest ratio of peak systolic pressure to end-systolic volume (i.e. the sickest patients) had the greatest improvement in stroke volume with nitroprusside (Figure 9). Thus, the sickest patients have the best response to nitroprusside. While patients with low blood pressures can become hypotensive on this agent, it is so short acting that it can be turned off and the effect be gone in a couple of minutes.



Heesch and Eichhorn. Am J Cardiol 1994; 74: 951-954.

Figure 9

Inotropic agents- There are three types of inotropic agents clinically available to treat acute heart failure, digitalis agents, non-digitalis inotropes (ß-agonists, PDE inhibitors), and pressors (α,ß-agonists, high dose dopamine).

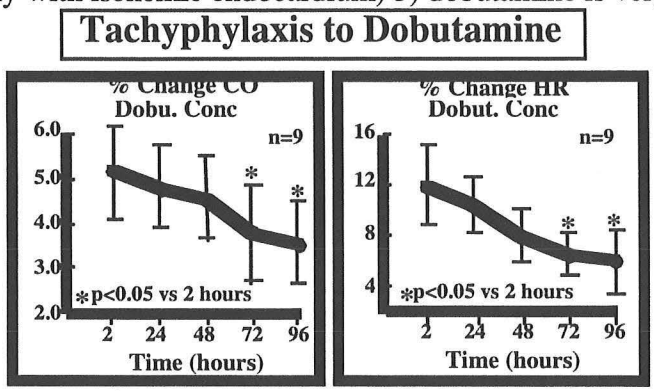
Digoxin- Digitalis agents such as digoxin are weak inotropic agents, but also have other properties.[32,33] Inhibition of the sodium-potassium ATPase pump in baroreceptors may result in a "resetting" of the receptors resulting in inhibition of sympathetic discharge.[34] This produces a reduction in sympathetic tone in the vasculature causing systemic vascular resistance to fall. Thus, digoxin is also a weak sympatholytic agent while providing weak inotropic support. Digitalis compounds have also been shown to improve myocardial relaxation in patients with mixed systolic and diastolic dysfunction.[19] This effect is probably due to increased elastic recoil as the effect of digoxin is to increase intracellular calcium flux. The net effect of digoxin is an increase in stroke volume and a reduction in wedge pressure.[35]

Recent studies of digoxin have demonstrated that the neurohormonal and hemodynamic benefits of digoxin are at a lower dose of digoxin, with little additional benefits at higher doses.[36] In addition, a post hoc analysis of the DIG study suggests a relationship between baseline serum digoxin concentrations and risk of death.[32] In this empirical observation, the risk of death increased significantly above a digoxin level of 1.0 ng/ml. While this relationship is not cause and effect since a higher plasma concentration may only reflect worse cardiac and renal function at baseline, a similar relationship between serum digoxin concentrations and mortality was observed in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial where a serum digoxin concentration > 1.1 ng/ml was associated with a 38% excess mortality rate.[37] In addition, digoxin is known to be arrhythmogenic at higher plasma concentrations.[38-40] This may be of most concern when higher doses of digoxin are used in patients with advanced coronary artery disease and ongoing ischemia. Myocardial ischemia itself may cause inhibition of sodium-potassium ATP-ase and render myocardial tissue more sensitive to the arrythmogenic effects of digitalis even at lower serum concentration.[41-44] Since reduction in worsening heart failure is seen with low dose digoxin and higher doses may provide little or no additional hemodynamic or neurohormonal benefit [36] (but do offer a higher risk of arrhythmia) [37-44], a dose that results in a serum concentration of 0.7-1.0 ng/ml may be preferable. The only exception to this might be patients who have atrial fibrillation and acute heart failure where rate control is necessary and acute beta-blockade cannot be initiated.

Non-digitalis inotropes- These agents primarily work by increasing the intracellular second messenger, cAMP.[45-47] This may be done by one of two methods: 1) stimulation of ß-adrenergic receptors (ß-agonists) or 2) preventing cAMP degredation (phosphodiesterase inhibition). Examples of ß-agonists include dobutamine, isoproterenol, and low dose dopamine. Examples of phosphodiesterase inhibitors (PDE III inhibitors) include amrinone and milrinone.

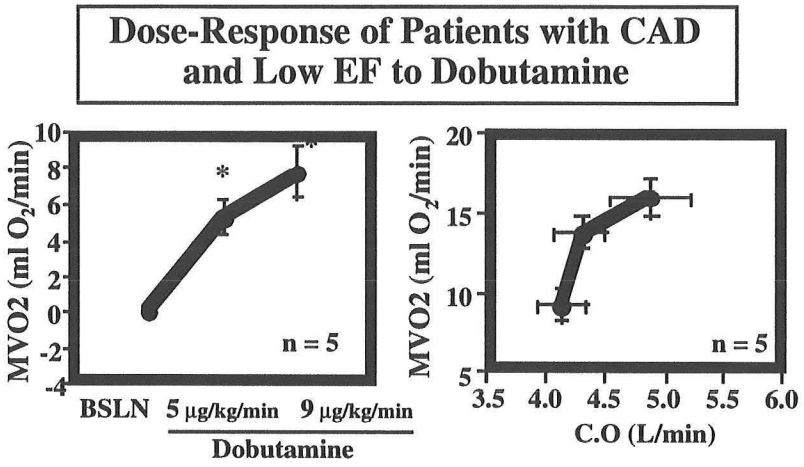
ß-agonists increase contractility, relaxation, and cause some modest vasodilation by either stimulation of $ß_2$ receptors (dobutamine, isoproterenol) or by stimulation of peripheral dopaminergic (DA_1) receptors (dopamine). The classic agent to use for heart failure is dobutamine.[29,48-59] Dobutamine is very good at increasing stroke volume, but only has modest effects on reducing pulmonary capillary wedge pressure.[29,50] Thus, it has to be combined with a vasodilator (such as nitroprusside) or diuretic in order to reduce filling pressures. In addition, dobutamine (as well as other ß-agonists) has several limitations: 1) tachyphylaxis develops within 72 hours (probably due to further ß-receptor downregulation)(Figure 10) [60,61] 2) dobutamine increases myocardial oxygen consumption

in a dose-dependent fashion(Figure 11).[29,62] This may be especially important in situations where oxygen delivery is limited (in the presence of ongoing ischemia or dilated cardiomyopathy with ischemic endocardium) 3) dobutamine is very arrhythmogenic.[50]



Unverferth DV et al. Am J Med 1980; 69: 262-266.

Figure 10



Takaoka et al. Am Heart J 1997; 133: 283-289

Figure 11

Other ß-agonists (Figure 12) include isoproterenol, which has much more $ß_2$-mediated vasodilation than dobutamine and thus may reduce BP in the patient who already has a low blood pressure.[53] In addition, dopamine has direct stimulatory effect on ß-receptors while inhibiting presynaptic NE release.[50,51,53] Dopamine at low doses also stimulates DA_1 receptors in the kidney promoting direct vasodilation of this vascular bed and improving renal blood flow. At higher doses, dopamine stimulates $alpha_1$ receptors causing vasoconstriction and a pressor effect.

Adrenergic Receptor Activity of Sympathomimetic Amines

Agent	Alpha	ßeta$_1$	ßeta$_2$	DA$_1$
	Vasoconstriction	Inotropy	Vasodilation	Vasodilation
Norepinephrine	++++	++++	0	0
Epinephrine	++++	++++	++	0
Dopamine (LD)	+	+++	+++	++++
Dopamine (HD)	++++	++++	++++	++++
Isoproterenol	0	++++	++++	0
Dobutamine	+	++++	+	0
Methoxamine	++++	0	0	0

Sonnenblick EH et al. N Engl J Med 1979; 300: 18.

Figure 12

Phosphodiesterase inhibitors, such as amrinone and milrinone, have some distinct advantages over ß-agonists [29,63-72]: 1) Milrinone is less subject to tachyphylaxis from ß-receptor downregulation (Figure 13) [63] 2) Phosphodiesterase inhibition in the periphery leads to vasodilation producing afterload reduction.[63,64,72] This is much like combining dobutamine with nitroprusside. This leads to a greater reduction in wedge pressure and less effect on myocardial oxygen consumption (Figure 14).[63] 3) Milrinone is much more effective in the presence of ß-blocker therapy as milrinone is not as dependent on the presence of intact-unoccupied ß-receptors [73] 4) Milrinone reduces RV afterload better than dobutamine.[71] Despite the better energetics of milrinone [63], it is still very arrhythmogenic due to higher cAMP levels.[65]

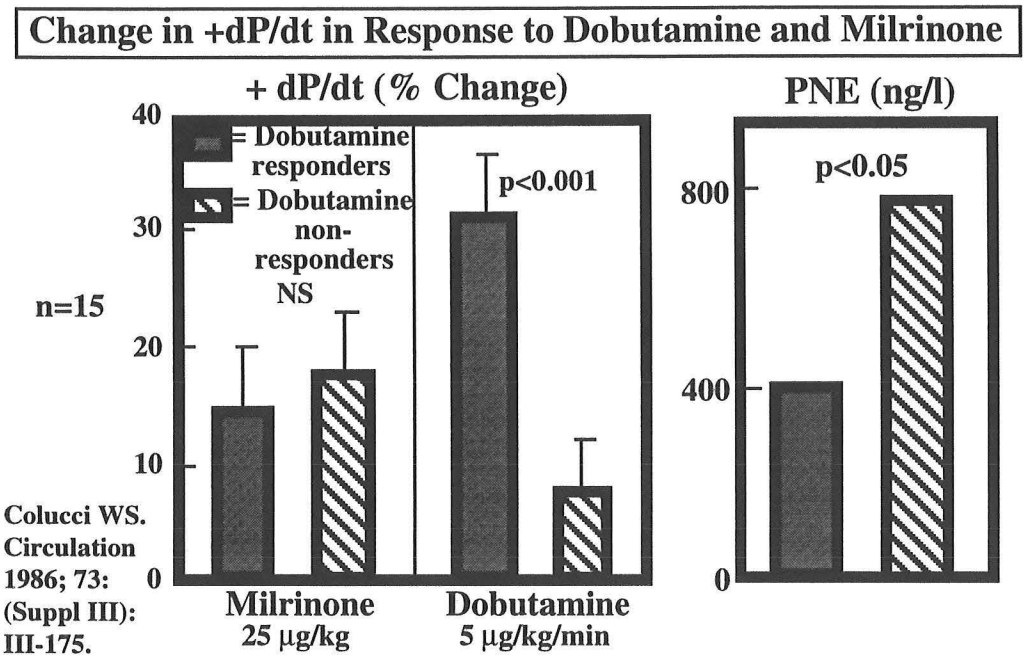
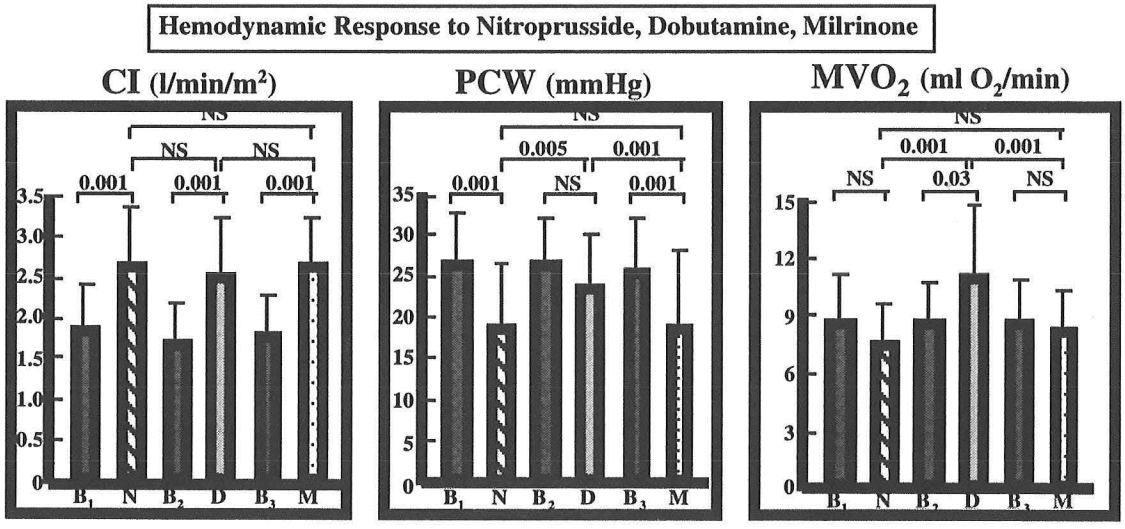


Figure 13



Monrad et al. Circulation 1986; 73 (Suppl III): III-168

Figure 14

Pressors- The prototypical pressor is norepinephrine (levophed). Other pressors include methoxamine and high dose dopamine.[53] Levophed increases BP by alpha$_1$ vasoconstriction. While BP increases, so does afterload and rate-pressure product. This theoretically results in: 1) increased myocardial oxygen consumption 2) little improvement in stroke volume as positive inotropic effects are counterbalanced by increased afterload 3) and can potentially result in ischemia in cardiac and non-cardiac tissues. Thus,

norepinephrine should be reserved for code situations or severe hypotension where re-establishment of a BP is critical.

Methoxamine is an alpha agonist without ß-agonist properties. While this will result in an increase in BP and afterload, it will also result in a reduction in stroke volume as inotropy is not augmented much while afterload is increased substantially.

High dose dopamine results in stimulation of the alpha receptors as well as ß-receptors. This produces both positive inotropy as well as vasoconstriction. Like norepinephrine, this produces an increase in BP and afterload that can result in ischemia and little improvement in stroke volume. Thus, high dose dopamine should be reserved for code situations or severe hypotension where re-establishment of a BP is critical.

Additional measures- In addition to pharmacologic therapy outlined, the patient may benefit from the following measures: 1) the patient should receive a 1.5-2 gm Na+ diet 2) any NSAIDS should be stopped as inhibition of renal production of prostacyclin in the afferent blood supply may result in vasoconstriction which can worsen renal perfusion (especially in the presence of ACE inhibitors and poor stroke volume to begin with) [74] 3) all calcium channel blockers (except amlodipine used to treat refractory hypertension or angina) should be stopped [75,76] 4) consider the need for revascularization in patients with severe coronary disease (especially if diastolic dysfunction prominent) 5) try to maintain sinus rhythm 6) consider mechanical devices (LVAD or IABP) as bridges to more definitive therapy or with the hope of remodeling the ventricle [77] 7) consider mitral repair [78] 8) consider transplant.

Summary- The treatment of acute heart failure must be designed to achieve the goal (reduce preload, improve stroke volume, maintain BP) at the least expense to energetics (MVO_2).

Medical Therapy for AHF

Agent	PCW	SV	HR	SBP	MVO_2	Effectiveness in presence of ß-blockers
Nitrates	↓↓↓	↑	↓	↓	↓↓	+++
Nitroprusside	↓↓	↑↑↑	↓↓	↓↓	↓↓↓↓	+++
Dobutamine	↓	↑↑↑↑	↑↑	↑	↑↑↑	+
Levophed	↑↑	↑	↑↑	↑↑↑	↑↑↑↑	+
Epinephrine	↑	↑↑	↑↑↑	↑↑	↑↑↑↑	+
Isoproterenol	↓	↑↑↑	↑↑↑	↓	↑↑	+
Dopamine (LD)	↑	↑	↑	↑↑	↑↑↑	+
Dopamine (HD)	↑↑	↑↑	↑↑	↑↑↑	↑↑↑↑	+
Milrinone	↓↓↓	↑↑↑↑	↑	↓	0	++

Figure 15

As is evident from Figure 15, nitrates, nitroprusside, and diuretics reduce pulmonary capillary wedge pressure (PCWP) without increasing MVO_2. In fact, MVO_2 falls in response to these agents due to reduced wall stress, making these energetically favorable interventions. If PCWP needs to be reduced and stroke volume is adequate (>25 ml/m2), diuretics would be the agent of choice. If PCWP is high and stroke volume is low, nitrates or nitroprusside should be used. These agents should be the first therapy given to reduce wedge pressure unless the patient has symptomatic hypotension (Figure 16). If this does not achieve the goal, then either dobutamine can be added to nitroprusside or milrinone can be given.

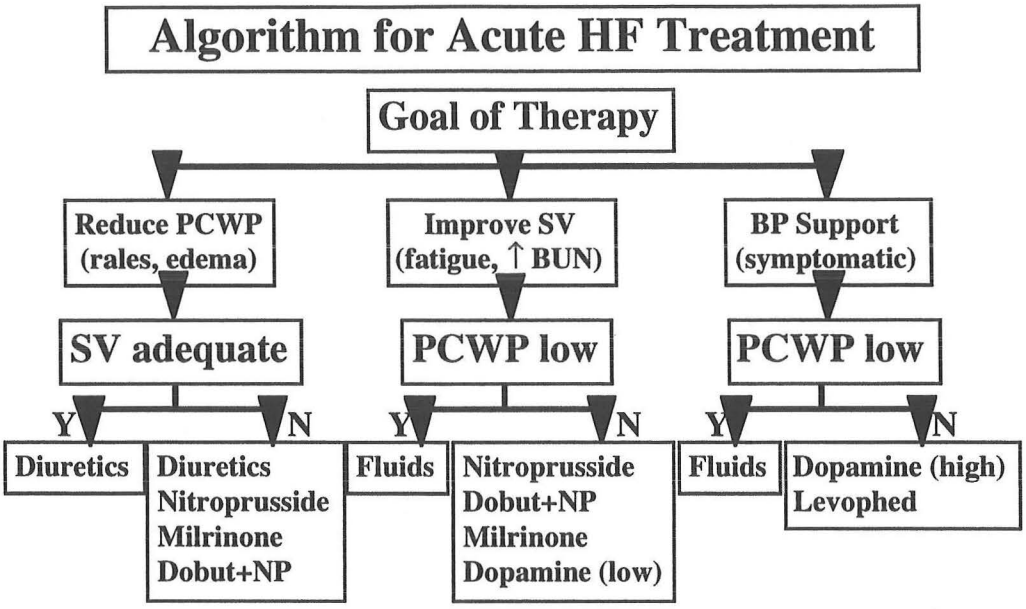


Figure 16

If the goal is to improve stroke volume, and the PCWP is low (<10 mmHg), fluids should be given to reach a PCWP of 15 to 18 mmHg. If PCWP is adequate (i.e. > 20 mmHg), nitroprusside will improve stroke volume without increasing MVO_2. Thus, this agent should be the first therapy given to improve stoke volume unless the patient has symptomatic hypotension (Figure 16). If this does not achieve the goal, then either dobutamine can be added to nitroprusside or milrinone can be given. Low dose dopamine can be added to maintain renal perfusion in cases where low stroke volume has resulted in elevations in BUN and creatinine.

If the goal is to maintain BP in a patient with SYMPTOMATIC hypotension (altered mentation, oliguria, shock), dopamine moderate to high doses should be used. If the patient is unresponsive, norepinephrine can be used. However, norepinephrine can result in limb and cardiac ischemia, increased afterload, and arrhythmias.

References

1. Eichhorn EJ, Bristow MR. Medical therapy can improve the biologic properties of the chronically failing heart: A new era in the treatment of heart failure. Circulation 1996; 94: 2285-2296.

2. Lowes BD, Minobe W, Abraham WT, Rizeq MN, Bohlmeyer TJ, Quaife RA, Roden RL, Dutcher DL, Robertson AD, Voelkel NF, Badesch DB, Groves BM, Gilbert EM, Bristow MR. Changes in gene expression in the intact human heart. Downregulation of α-myosin heavy chain in hypertrophied, failing ventricular myocardium. J Clin Invest 1997; 100: 2315-2324.

3. Bristow MR, Gilbert EM, Lowes BD, Minobe WA, Shakar SF, Quaife RA, Abraham WT. Changes in myocardial gene expression associated with ß-blocker-related improvement in ventricular systolic function. Circulation 1997; 96: I-92. Abstract.

4. Packer M, Carver JR, Chesebro JH, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, Mallis GI, Sollano JA, Shannon J, Tandon PK, DeMets DL and the PROMISE investigators. Effect of milrinone on mortality in severe chronic heart failure. The prospective randomized milrinone survival evaluation (PROMISE). N Engl J Med 1991; 325: 1468-1475.

5. Packer M, Rouleau J, Swedberg K, Pitt B, Fisher L, Klepper M, and the PROFILE Investigators & Coordinators. Effect of flosequinan on survival in chronic heart failure: Preliminary results of the PROFILE study. Circulation 1993; 88 (Suppl I): I-301. Abstract.

6. The xamoterol in severe heart failure study group. Xamoterol in severe heart failure. Lancet 1990; 336: 1-6.

7. Dies F, Krell MJ, Whitlow P, Liang C, Goldenberg I, Applefeld MM, Gilbert EM. Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. Circulation 1986; 74 (Suppl II): II-38. Abstract.

8. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky B, McNulty SE, Darius H, Schulman K, Zannad F, Handberg-Thurmond E, Harrell FE, Wheeler W, Soler-Soler J, Swedberg K. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997; 134: 44-54.

9. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, Shelton B, for the SOLVD Investigators. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD Echocardiography Substudy. Circulation 1995; 91: 2573-2581.

10. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time Course of Improvement in Left Ventricular Function, Mass, and Geometry in Patients with Congestive Heart Failure Treated with ß-Adrenergic Blockade. J Am Coll Cardiol 1995; 25: 1154-61.

11. Hasford J, Ansari H, Lehmann K. CART and logistic regression analyses of risk factors for first dose hypotension by an ACE-inhibitor. Therapie 1993; 48: 479-82.

12. Eichhorn EJ, Bristow MR. Practical Guidelines for Initiation of ß-adrenergic Blockade in Patients with Chronic Heart Failure. Am J Cardiol 1997; 79: 794-798.

13. Ross J, Braunwald E. Studies on Starling's law of the heart: the effects of impeding venous return on performance of the normal and failing human left ventricle. Circulation 1964;30:719-727.

14. Borow KM, Green LH, Grossman W, Braunwald E. Left ventricular end-systolic stress-shortening and stress-length relations in humans. Normal values and sensitivity to inotropic state. Am J Cardiol 1982; 50: 1301-1308.

15. Suga, H and Sagawa, K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circulation Res 1974; 35: 117-126.

16. Grossman, W, Braunwald, E, Mann, T, McLaurin, LP, and Green, LH. Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations. Circulation 1977; 56: 845-852.

17. Mehmel, HC, Stockins, B, Ruffmann, K, Olshausen, K, Schuler, G, and Kubler, W. The linearity of the end-systolic pressure-volume relationship in man and its sensitivity for assessment of left ventricular function. Circulation 1981; 63: 1216-1222.

18. Gilbert JC, Glantz SA. Determinants of left ventricular filling and of the diastolic pressure-volume relation. Circ Res 1989; 64: 827-852.

19. Eichhorn EJ, Willard JE, Alvarez L, Kim AS, Glamann DB, Risser RC, Grayburn PA. Are contraction and relaxation coupled in patients with and without congestive heart failure? Circulation 1992; 85: 2132-2139.

20. Poole-Wilson PA. "Diuretics for the Treatment of Heart Failure" in Congestive Cardiac Failure: Pathophysiology and Treatment. Barnett DB, Pouleur H, and Francis GS and eds. New York: Marcel Dekker, Inc., 1993, pp. 103-117.

21. Rudy DW, Gehr TWB, Matzke GR, Kramer WG, Sica DA, Brater C. The pharmacodynamics of intravenous and oral torsemide in patients with chronic renal insufficiency. Clin Pharmacol Ther 1994; 56: 39-47.

22. Dormans TPJ, van Meyel JJM, Gerlag PGG, Tan Y, Russel FGM, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: Bolus injection versus continuous infusion. J Am Coll Cardiol 1996; 28: 376-82.

23. Epstein M, Lepp BA, Hoffman DS, et al. Potentiation of furosemide by metolazone in refractory edema. Current Therapeutic Research 1977; 21: 656-667.

24. Packer M, Gottlieb SS, Kessler PD. Hormone-electrolyte interactions in the pathogenesis of lethal cardiac arrhythmias in patients with congestive heart failure. Am J Med 1986; 80 (Suppl 4A): 23-29.

25. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987; 57: 17-22.

26. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang C, Kubo SH, Rudin-Toretsky E, Yusuf S. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. Circulation 1990; 82: 1724-1729.

27. Heesch CM, Hatfield BA, Marcoux L, Eichhorn EJ. Predictors of pressure and stroke volume response to afterload reduction with nitroprusside in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol 1994; 74: 951-954.

28. Hasenfuss G, Holubarsch C, Heiss HW, Meinertz T, Bonzel T, Wais U, Lehmann M, Just H. Myocardial energetics in patients with dilated cardiomyopathy. Influence of nitroprusside and enoximone. Circulation 1989; 80: 51-64.

29. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. Circulation 1986; 73 (Suppl III): III-168-III-174.

30. Eichhorn EJ, Hatfield B, Marcoux L, Risser RC. Functional importance of myocardial relaxation in patients with congestive heart failure. J Card Failure 1994; 1: 45-56.

31. Weiland DS, Konstam MA, Salem DN, Martin TT, Cohen SR, Zile MR, Das D. Contribution of reduced mitral regurgitant volume to vasodilator effect in severe left ventricular failure secondary to coronary artery disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1986; 58:1046-50.

32. Gheorghiade M, Pitt B. Digitalis Investigation Group (DIG) trial: A stimulus for further research. Am Heart J 1997; 134: 3-12.

33. Gheorghiade M. Digoxin. Cardiology Clinics: Annual of Drug Therapy 1997; 1: 81-103.

34. Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienzle MG. Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. Circulation 1989; 80: 65-77.

35. Arnold SB, Byrd RC, Meister W, et al. Long-term digitalis therapy improves left ventricular function in heart failure. N Engl J Med 1980; 303: 1443-8.

36. Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn RA, Eichhorn EJ. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? J Am Coll Cardiol 1997; 29: 1206-1213.

37. Mancini DM, Benotti JR, Elkayam U, et al for the PROMISE Investigators and Coordinators. Antiarrhythmic drug use and high serum levels of digoxin are independent adverse prognostic factors in patients with chronic heart failure. Circulation 1991; 84: II-243. Abstract.

38. Smith TW, Antman EM, Friedman PL, Blatt CM, Marsh JD. Digitalis glycosides: Mechanisms and manifestations of toxicity. Prog Cardiovasc Dis 1984; 26: 413-458 and 495-530.

39. Smith TW, Haber E. Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration. J Clin Invest 1970; 49: 2377-86.

40. Beller GA, Smith TW, Abelmann WH, Haber E, Hood WB. Digitalis intoxication: A prospective clinical study with serum level correlations. N Engl J Med 1971; 284: 989-997.

41. Beller GA, Conroy J, Smith TW. Ischemia-induced alterations in myocardial (Na^+-K^+)-ATPase and cardiac glycoside binding. J Clin Invest 1976; 57: 341-350.

42. Tanz RD, Russel NJ, Banerian SP, et al. Ouabain-induced tachyarrythmias and cell damage in isolated perfused guinea-pig hearts: Protection by propranolol. J Mol Cell Cardiol 1982; 14: 655-671.

43. Lynch JJ, Montgomery DG, Lucchesi BR. Facilitation of lethal ventricular arrhythmias by therapeutic digoxin in conscious postinfarction dogs. Am Heart J 1986; 111: 883-890.

44. Lynch JJ, Kitzen JM, Hoff PT, Lucchesi BR. Reduction in digitalis-associated postinfarction mortality with nadolol in conscious dogs. Am Heart J 1988; 115: 67-76.

45. Feldman AM, Bristow, MR. Adrenergic neuroeffector mechanisms in the failing human heart in *Heart Disease (Update). A textbook of cardiovascular medicine 3rd edition.* Braunwald E (ed.) . Philadelphia: W.B. Saunders Co., 1990.

46. Bristow MR, Hershberger RE, Port JD, Gilbert EM, Sandoval A, Rasmussen R, Cates AE, Feldman AM. ß-adrenergic pathways in nonfailing and failing human ventricular myocardium. Circulation 1990; 82 (Suppl I): I-12-I-25.

47. Eichhorn EJ. "The paradox of beta-adrenergic blockers for the management of congestive heart failure." in Congestive Heart Failure: Pathophysiology and Treatment. Barnett DB, Pouleur H, and Francis GS and eds. New York: Marcel Dekker, Inc., 1993, pp. 213-250.

48. Colucci WS, Leatherman GF, Ludmer PL, Gauthier DF. ß-adrenergic inotropic responsiveness of patients with heart failure: Studies with intracoronary dobutamine infusion. Circ Res 1987; 61 (Suppl I): I-82-I-86.

49. Little WC, Rossi Jr, Freeman GL. Comparison of effects of dobutamine and ouabain on left ventricular contraction and relaxation in closed-chest dogs. J Clin Invest 1987; 80: 613-620.

50. Leier CV, Heban PT, Huss P, Bush CA, Lewis RP. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation 1978; 58: 466-475.

51. Stoner JD, Bolen JL, Harrison DC. Comparison of dobutamine and dopamine in treatment of severe heart failure. Brit Heart J 1977; 39: 536-539.

52. Tuttle RR, Mills J. Dobutamine. Development of a new catecholamine to selectively increase cardiac contractility. Circ Res 1975; 36: 185-196.

53. Sonnenblick EH, Frishman WH, LeJemtel TH. Dobutamine: A new synthetic cardioactive sympathetic amine. N Engl J Med 1979; 300: 17-22.

54. Colucci WS, Denniss R, Leatherman GF, Quigg RJ, Ludmer PL, Marsh JD, Gauthier DF. Intracoronary infusion of dobutamine to patients with and without severe congestive heart failure. J Clin Invest 1988; 81: 1103-1110.

55. Leier CV, Unverferth DV. Dobutamine. Ann Intern Med 1983; 99: 490-496.

56. Cote P, Bourassa MG, Tubau JF, Enjalbert M, Vandormael M. Effects of dobutamine on left ventricular performance and myocardial metabolic demands in patients with ischemic heart disease. Clin Cardiol 1984; 7: 14-22.

57. Akhtar N, Mikulic E, Cohn JN, Chaudhry MH. Hemodynamic effect of dobutamine in patients with severe heart failure. Am J Cardiol 1975; 36: 202-205.

58. Unverferth DV, Magorien RD, Altschuld R, Kolibash AJ, Lewis RP, Leier CV. The hemodynamic and metabolic advantages gained by a three-day infusion of dobutamine in patients with congestive cardiomyopathy. Am Heart J 1983; 106: 29-34.

59. Maekawa K, Liang C-S, Hood WB. Comparison of dobutamine and dopamine in acute myocardial infarction. Effects of systemic hemodynamics, plasma catecholamines, blood flows and infarct size. Circulation 1983; 67: 750-759.

60. Unverfirth DV, Blanford M, Kates RE, Leier CV. Tolerance to dobutamine after a 72 hour continuous infusion. Am J Med 1980; 69: 262-266.

61. Colucci WS, Alexander RW, Williams GH, Rude RE, Holman BL, Konstam MA, Wynne J, Mudge GH, Braunwald E. Decreased lymphocyte beta-adrenergic-receptor density in patients with heart failure and tolerance to the beta-adrenergic agonist pirbuterol. N Engl J Med 1981; 305: 185-90.

62. Takaoka H, Takeuchi M, Hata K, Hayashi Y, Mori M, Yamakawa H, Yamaguchi K, Yokoyama M. Beneficial effects of a Ca2+ sensitizer, MCI-154, on the myocardial oxygen consumption-cardiac output relation in patients with left ventricular dysfunction after myocardial infarction: comparison with dobutamine and phosphodiesterase inhibitor. Am Heart J 1997; 133: 283-289.

63. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. Circulation 1986; 73 (Suppl III): III-175-III-183.

64. Karlsberg RP, DeWood MA, DeMaria AN, Berk MR, Lasher KP, for the Milrinone-Dobutamine Study Group. Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction. Clin Cardiol 1996; 19: 21-30.

65. Pflugfelder PW, O'Neill BJ, Ogilvie RI, Beanlands DS, Tanser PH, Tihal H, Mizgala HF, Fitchett DH, Kostuk WJ. A Canadian multicentre study of a 48 h infusion of milrinone in patiens with severe heart failure. Can J Cardiol 1991; 7: 5-10.

66. Anderson JL for the United States Milrinone Multicenter Investigators. Hemodynamic and clinical benefits with intravenous milrinone in severe chronic heart failure: Results of a multicenter study in the United States. Am Heart J 1991; 121: 1956-64.

67. Seino Y, Momomura S-I, Takano T, Hayakawa H, Katoh K for the Japan Intravenous Milrinone Investigators. Multicenter, double-blind study of intravenous milrinone for patients with acute heart failure in Japan. Crit Care Med 1996; 24: 1490-1497.

68. Cusick DA, Pfeifer PB, Quigg RJ. Effects of intravenous milrinone followed by titration of high-dose oral vasodilator therapy on clinical outcome and rehospitalization rates in patients with severe heart failure. Am J Cardiol 1998; 82: 1060-1065.

69. Mager G, Klocke RK, Kux A, Hopp H-W, Hilger HH. Phosphodiesterase III inhibition or adrenoreceptor stimulation: Milrinone as an alternative to dobutamine in the treatment of severe heart failure. Am Heart J 1991; 121: 1974-83.

70. Konstam MA, Cody RJ. Short-term use of intravenous milrinone for heart failure. Am J Cardiol 1995; 75: 822-826.

71. Eichhorn EJ, Konstam MA, Weiland DS, Roberts DJ, Martin TT, Stransky NB, Salem DN. Differential effects of milrinone and dobutamine on right ventricular preload, afterload, and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1987; 60: 1329-1333.

72. Jaski BE, Fifer MA, Wright RF, Braunwald E, Colucci WS. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure: Dose-response relationship and comparison to nitroprusside. J Clin Invest 1985; 75: 643-649.

73. Tsvetkova T, Farber DJ, Abraham WT, Kelley P, Eichhorn EJ, Gilbert EM, Robertson AD, Lindenfeld J, Wolfel E, Zisman L, Bristow MR, Lowes BD. Comparative hemodynamic effects of milrinone and dobutamine in heart failure patients treated chronically with carvedilol. Heart Failure Society of America 1998 (unpublished).

74. Dzau VJ, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe heart failure: relation to activation of the renin-angiotensin system and hyponatremia. N Engl J Med 1984; 310: 347-352.

75. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990; 82: 1954-1961.

76. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S, the Adverse Experience Committee and the Multicenter Diltiazem Postinfarction Research Group. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. Circulation 1991; 83: 52-60.

77. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. N Engl J Med 1998; 339: 1522-33.

78. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. J Thorac Cardiovasc Surg 1998;115: 381-6.