# New Hope for the Failing Heart

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KALP YETMEZLİĞİNDE YENİ ÜMİTLER

ABD halkının altıda birinde kalp ve damar hastalığı mevcuttur. Tahminen 3,5-4 milyon Amerikalı kronik kardiak yetmezlikten muzdariptir. Kalp yetmezliğinin yol açtığı kişisel ve toplumsal kayıplar büyüktür. Digital ve diüretiklerle standart medikal tedavi, çoğu kez kötü gidişli bu hastalıkla ilgili morbiditeyi kontrol etmekte genellikle yetersizdir. Bu yüzden daha etkin bir medikal tedaviye gerek vardır. Yeni geliştirilmiş kuvvetli, oral olarak aktif kardiotonik ajanlar bu ihtiyaca cevap verebilir. Günümüzde yeni kardiotonik ajanlar henüz araştırma dönemindedir. **II.** ve **III.** faz klinik denemeler bu ajanlann etki ve güvenirliği konusunda henüz başlangıçta veya yeni tamamlanmak üzeredir, Ventrikül fonksiyonu hakkında objektif parametreler ve hastanın yaşam standardı iyicf kontrol edilmelidir. Uzun süren tedavi ile myokardm bu ajanlardan yararlanmasının mümkün olup olmayacağı konusunda bilgi toplanmaktadır. Bu çalışmalarla kuvvetli inotropik özelliklere sahip bileşiklerin varlığı, klinik kardiyolojide büyük heyecan ve sevince yol açmıştır. Çünkü kronik kalp yetmezlikli hastaların daha etkili tedavisinin gerçekleşebilirliği ufukta gözükmektedir. Gerçekten de kalp yetmezliği konusunda yeni umutlar taşımaktadır.

**Digitalis and diuretics are oftentimes inadequate to ameliorate the morbidity associated with chronic cardiac failure. Patients who are not candidates for remedial surgery and whose symptomatic heart failure defies standard medical therapy require more effective treatment. Suitable candidates for cardiac transplantation in whom there can be high expectation for success have been estimated to number from only several hundred to 3,000 annually[1], leaving many patients without much hope. During the past several years, however, the pharmaceutical industry has developed a variety of drugs that may indeed prove helpful. These compounds include oral cardiotonic agents having potent inotropic properties to assist the failing myocardium and specific vasodilators (e.g., the angiotensin converting enzyme inhibitors and *a*\ adrenergic receptor blockers) to reduce the workload of the overburdened heart.**

**The use of vasodilators in the treatment of cardiac failure has been reviewed elsewhere[2-7]. By reducing the heightened impedance of the arterial circulation that accompanies heart failure, vasodilators indirectly improve the pumping function of the failing heart (Figure 1). However, while many patients show improvement during vasodilator therapy, the resultant augmentation in systemic flow and its reapportionment may not be optimal. For example, cutaneous or splanchic flow may increase[4] at the expense of coronary perfusion[5]. Similarly, the increment in skeletal muscle flow required during exercise may be thwarted[4]. These considerations and the mechanisms involved in the development of tolerance to vasodilators has recently been reviewed by Colucci and coworkers[8]. The ultimate efficacy and safety of these agents, therefore, must await the results of controlled clinical trials. Moreover, as one patient with heart failure, who failed to improve after a trial of several vasodilators, was heard to say, "taking one's foot off the hose will not let you adequately drain a flooded basement if the pump is no good." Hence, there is a**

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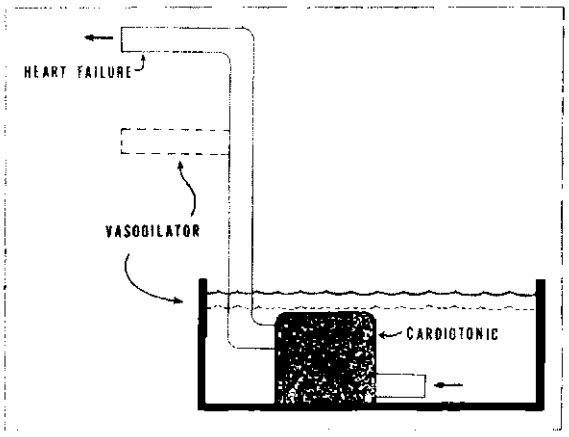


**Figure 1.** The management of congestive heart failure may be likened to the clearing of a flooded basemen with a sump pump. In heart failure, a weak pump an reduced cardiac output are accompanied by arteriolar vasoconstriction, reapportioned systemic flow and venous congestion. The heightened impedance of the arterial circulation is analogous to an increase in the level of the outflow conduit from the sump pump, while organ congestion may be likened to be degree of flooding in the basement. Vasodilators, by promoting arteriolar vasodilation, reduce the height of the conduit and therefore the hydrostatic load on the pump. Pharmacologically induced venodilation would lower the hydrostatic level in the basement. These effects, which indirectly improve the performance of the weakened pump, may not always be adequate or desirable. Cardiotonic agents act directly on the pump to augment is performance an effect akin to installing a more powerful pump.

**need to directly improve the function of the pump.**

**Cardiotonic agents act directly on the failing myocardium to augment is contractile state and improve pump function. Systemic flow is therefore augmented and apportioned to each organ according to the autoregulatory behavior of its vascular bed. The major question here, however, is whether or not a chronic increment in contractility would prove harmful to the failing heart. The purpose of this report will be to review the evolving experience with new oral cardiotonic agents currently under active investigation in the long-term treatment of chronic cardiac failure. First, however, a few words are in order concerning the evaluation required by the Food and Drug Administration before any new cardiotonic drug can be marketed.**

## CLINICAL TRIALS. EFFICACY AND SAFETY OF CARDIOTONIC AGENTS

**After the development of a new compound and the demonstration of its positive inotropic properties in the experimental laboratory, the drug must successfully complete a series of clinical trials. Three phases of clinical investigation are required. Phase I trials are designed to evaluate the safety of the compound in a small number of healthy volunteers. Attention is also given to the issue of drug tolerance, absorption, metabolism and interaction with other drugs. Phase II trials are designed to determine the efficacy and safety of the cardiotonic agent in patients with cardiac failure. Patients with severe cardiac failure, requiring treatment in the intensive care unit, will oftentimes be the first to receive the drug. The hemodynamic response of the failing heart and the effective dosage range are specific objectives of this phase, whereas double-blind controlled trials are initiated at several medical centers in the later stages of phase II trials. Finally, in Phase III trials, the safety of the compound is determined in several hundred patients with chronic, stable cardiac failure who received the drug for six to 12 months at many different centers across the country. Adverse effects are closely monitored and dosage range is refined. Studies that profile the response of special groups of patients, such as the elderly or those with acute myocardial infarction, or that address relevant questions (e.g., the Influence of the cardiotonic agent on myocardial oxygen utilization in patients with coronary artery disease) are also undertaken.**

**Several years are required to complete these trials It should be apparent that despite an early experience reporting a favorable hemodynamic response to a new drug, there is no guarantee that it will ultimately prove effective and safe. Encouraging results seen in small numbers of patients during the early stages of Phase II testing must therefore be interpreted with appropriate caution. Contrariwise, adverse effects that may be observed in critically ill patients, who require unusually large quantities of the agent or in whom plasma levels of the compound or its metabolite are excessive because of oliguria, may not be entirely representative.**

## CARDIOTONIC AGENTS AND MANAGEMENT OF CHRONIC CARDIAC FAILURE

**The goal of any treatment for the failing heart is to enhance ventricular emptying. This will raise cardiac output and oxygen delivery to the metabolizing tissues while reducing ventricular filling pressure and organ congestion. Oxygen delivery must be improved at rest as well as during the increased oxygen requirements attendant with physical activity.**

**Physiologic** Rationale. **The myocardium is composed of cardiac muscle fibers tethered within an extensive network of connective tissue. Conceptually, the myocardium may therefore be veiwed as a muscular pump The output of the pump is determined by a variety of factors, including the contractile state of its muscle fi hers'. Contractility and contractile state are terms used to describe that property of cardiac muscle that determines the force and speed of muscle contraction independently of muscle length or the load against which muscle has to shorten (i.e., the afterload). An augmentation in myocardial contractility is accompanied by greater muscle fiber shortening and, thereby, increased ventricular emptying.**

**At the cellular level, contractility is governed by**

the Ca released at the actomyosin junction . The mechanisms whereby this may occur have not been precisely defined. Nevertheless, a grossly simplified view of extra-and intracellular Ca* movement can be developed to depict the influence of cardiotonic agents on these processes. Such a view is given in Figure 2.

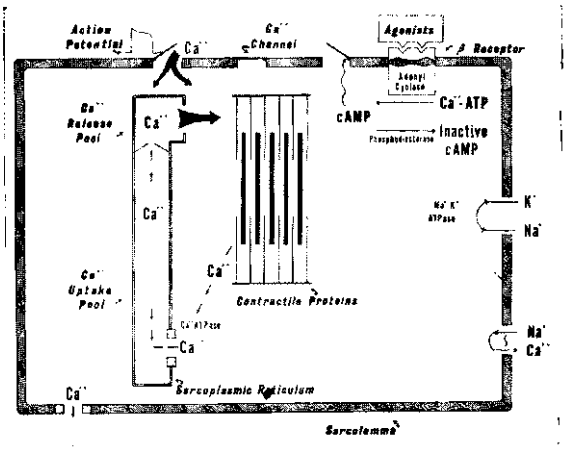


Figure 2. A simplified schematic of myocardial $Ca^{++}$ kinetics. During depolarization, $Ca^{++}$ enters the cell through $Ca^{++}$ channels. This Ca current becomes available to the contractile proteins and also stimulates the release of stored Ca from the sarcoplasmic reticulum. The number of open Ca channels ma| be determined by intracellular cyclic AMP (cAMP). Ca movement across the sarcolemma is also regulated by a $Na^{+}$-$Ca^{++}$ : counter-transport system. See text for how cardiotonic agents augment myocardial contractility by raising the Ca available to the contractile proteins.

Extracellular Ca (10 M) moves across the sarcolemma and down a concentration gradient into the intracellular space (10 M) through voltage-dependent Ca* channels. Ca movement across the sarcolemma is also regulated by an electrically neutral Na - Ca* exchange counter - transport system in which two to four Na ions are exchanged for one Ca* ion. Within the cell, there are also Ca* concentration gradients. The Ca* concentration of the intracellular membrane system, the sarcoplasmic reticulum, for example, is higher (10"^M) than the cytosol. One component of the Ca* stored in the sarcoplasmic reticulum is termed the Ca* release pool; it provides Ca* to the contractile proteins when Ca* channels open during depolarization. The resultant influx of Ca* serves as a current to promote the release of stored Ca . The other component of the stored Ca*, called the Ca* uptake pool, derives its Ca* from they cytosol. An ATP-dependent Ca* pump within the sarcoplasmic reticulum is responsible for moving Ca against the chemical gradient and into the uptake pool. Cardiotonic agents with a recognized mechanism of action augment myocardial contractility by increasing the Ca available to the contractile proteins by perturbing one of these processes involved in Ca* movement.

Na -K - ATPase Inhibition. The cardiac glycosides bind with the Na^-K'"- ATPase membrane transport system and inhibit its function, reducing the transmembrane exchange of Na and K . As a result, intracellular Na is increased, which, in turn, inhibits Na and Ca* exchange to raise intracellular. Ca* concentration. Controversy, however surrounds the specific nature of events involved in digitalis-induced alteration in Ca* kinetics .

Because of its narrow therapeutic-to-toxic ratio and limited plasma concentration, the inotropic effects of digitalis are relatively modest and oftentimes inadequate to sustain the failing heart. Symptoms of cardiac failure often persist despite digitalis and diuretic therapy. These patients are said to have "refractory" heart" failure, implying that the myocar dium is no longer responsive to inotropic stimuli. The fact that potent cardiotonic agents such as dobutamine, dopamine and amrinone will augment cardiac performance in thes epatients indicates that the myocardium is indeed responsive. Standard medical therapy, however, is simply inadequate.

cAMP Production. Sympathomimetic amines bind reversibly to ^-adrenergic receptor sites on the cardiac cell surface activating adenyl cyclase and raising intracellular cAMP production. Other cardiotonic agents (e.g., glucagon or xanthines) have the capacity to increase intracellular cAMP without involving the p receptor as will be indicated below. The intracellular concentration of cAMP may regulate the number of active or open Ca* channels; raising cAMP production would therefore recruit more of these channels.

j3- Adrenergic Receptor Agonists. The adrenergic receptors located in the heart that regulate myocardial contractile state have been termed *p*, while those receptors that promote tracheal or vascular smooth muscle relaxation are termed ft . Controversy, however, surrounds this simplistic classification, as well as the issues of receptor typing according to end organ, the relative distribution of receptors within an organ and the manner in which compounds may differ in their effects on chrono- and inotropic response (both presumably j3j effects).

The sympathomimetic amines are p\ receptor agonists. The potent inotropic properties of the catecholamines are well recognized. Because they must be administered parenterally, their clinical usefulness has been limited to the treatment of hospitalized patients Innovative new techniques, such as microcomputerized infusion pumps or transdermal absorption, may provide more effective methods with which to deliver catecholamines, such as dobutamine with its dose-dependent p\ and ^2 agonistic properties, to non hospitalized patients.

A number of oral β- adrenergic agonists have been developed. The relative selectivity of their (inotropic) and *&2* (vasodilator) properties is unclear at the present time. Prenalterol is a /3-adrenergic ago-

nist[16] that is effective when given orally or parenterals. In both normal volunteers[1] and patients with heart disease[18,19], short-term administration of prenalterol was found to augment left ventricular performance However, a significant increase in the frequency of ventricular ectopic contractions has been reported[20] A greater incidence of isolated ventricular and supraventricular contractions was also noted in volunteers receiving prenalterol[17]. After six days, Waagstein et al[21]. have reported a favorable clinical response to oral prenalterol therapy. Experience with this agent in the long-term management of patients with chronic cardiac failure has not yet been reported.

Pirbuterol is a new oral /5 receptor agonist that has both vasodilator and positive inotropic properties[22]. In patients with chronic cardiac failure, pirbuterol has been shown to acutely improve ventricular function[23,24] and to an extent that compared favorably with dobutamine [5] without adversely raising myocardial oxygen consumption[26]. The long-term experience with pirbuterol, however, has been variable. Awan et al [7]. Found a sustained improvement in ventricular function and treadmill exercise duration after six weeks of therapy, as did Pamelia and co-workers[9] . Dawson and his colleagues[8] reported a significant and persistent improvement in hemodynamic function in 16 patients receiving pirbuterol for four months, while in 15 patients, pirbuterol had to be withdrawn due to a lack of efficacy (10 patients) or adverse effects (five patients). After one month of pirbuterol therapy, Colucci and co-workers[30] found that cardiac output and ejection fraction had returned to control levels after an initial improvement. These investigators also noted a decrease in j3-adrenergic receptor density of the lymphocytes in these patients, prompting them to suggest that the same response may also have occurred in the myocardium and vascular smooth muscle. During a seven-week controlled trial in 12 patients, we* could not demonstrate an improvement in clinical status, exercise performance or echocardiographic estimates of ventricular function in either the pirbuterol- or placebo- treated patients. This was also true after these patients were maintained on open pirbuterol therapy for an additional 12 weeks. The efficacy of pirbuterol in the long-term, management of chronic cardiac failure must therefore await the results of further controlled trials.

Salbutamol is another oral /J adrenergic receptor agonist that belongs to the isoproterenol family of drugs. Its intravenous administration has been found to improve ventricular pump function in patients with congestive cardiomyopathy, including an augmentation in the time derivative of left ventriculer pressure[31] The oral formulation of salbutamol has also been shown to acutely increase cardiac performance[32]. The efficacy and safety of this compound await the results of long-term clinical trials.

Butopamine is an oral (3 receptor agonist that is structurally related to dobutamine. And while its positive inotropic properties have been demonstrated in normal subjects [3], its choronotropic reporties and adverse influence in cardiac rhythm have prohibited its further development.

Ibopamine is the di-isobutyric ester ofN-methyldopamine. Its oral administration to human volunteers has resulted in enhanced urine output and $Na^+$ excretion with a significant alteration in arteral pressure or heart rate[34] [6]. Clinical trials with this compound in patients with heart failure have not been reported.

Glucagon and the Phosphodiesterase Inhibitors. Glucagon increases cAMP by direct activation of adenyl cyclase while the xanthines raise cAMP by inhibiting the cAMP-degrading enzyme phosphodiesterase. In patients with chronic cardiac disease, the hemodynamic response to glucagon has been variable[37] ; it has not been very effective in patients with severe heart failure. The modest increment in pump function following glucagon administration, together with troublesome gastrointestinal symptoms, have removed it from the current therapeutic scene.

At the turn of the century, caffeine, a phosphodiesterase inhibitor with weak cardiotonic and diuretic properties, was used to treat heart failure. More recently, a number of phosphodiesterase inhibitors with potent positive inotropic properties have been developed, including UK-14-275 and UK-31,557 (carbazeran), RMI 17-043 and RMI 19-205. The ultimate efficacy and safety of these compounds will have to be assessed in forthcoming clinical trials.

Unknown Mechanism of Action. The mechanism by which the bipyridine derivative amrinone augments myocardial contractile state is unknown[40]. Amrinone has not been found to inhibit the $Na^+$-K* -ATPase transport system and therefore it can be used in combination with digitalis in patients having atrial fibrillation. Pretreatment with reserpine or propranolol has not been shown to aller the inotropic properties of amrinone in isolated cat atria or papillary muscle, or the intact cat heart. Thus, the release of norepinephrine stores from within the myocardium or the stimulation of jS-adrenergic receptor sites is not contributory. Finally, amrinone has not been found to alter the cAMP concentration of isolated cat atria. The elucidation of amrinone's mechanism of action will prove most interesting and perhaps lead to a whole new understanding of the contractile process, as well as to the development of other potent cardiotonic agents.

Amrinone has been shown to improve ventricular function in patients with severe chronic cardiac failure [1] > .In patients with cardiac failure secondary to coronary artery disease, the salutory hemodynamic effects of amrinone were not accompanied by an increase in myocardial oxygen requirement[41]. Moreover, the short-term administration of amrinone has been shown to improve cardiac performance during treadmill exercise, while long-term therapy has been associated with a significant increase in aerobic capacity and exercise tolerance[14]. In a number of patients, we have found that radiographic heart size

was significantly reduced after 12 weeks of amrinone therapy.

In more than 200 patients treated with oral amrinone, observed adverse effects include transient asymptomatic thrombocytopenia (<. 100,000/mm ) in 18 percent, gastrointestinal symptoms in 23 percent, fever in 5 percent, five cases of abnormal liver function results and one case of diabetes insipidus[13,14,42]. Hence, while the early experience with amrinone appears to be quite encouraging, determination of its ultimate efficacy and safety must await the completion of controlled Phase III clinical trials.

Ionophores are naturally occurring antibiotics that modify the permeability of biologic membranes. These compounds from lipid-soluble complexes with cations and are, thereby, able to cross the cell membrane. Positive inotropic effects of the inophore RO 2-2985 has been reported in isolated cardiac muscle, intact heart and anesthetized dogs[43]. The mechanism of action by which contractility is increased and calcium flux altered by this compound is unclear. These effects, however, would be operative throughout the body, including vascular smooth muscle. Hence, it is uncertain whether the ionophores will prove useful in the treatment of clinical cardiac failure.

## PATIENT SELECTION FOR ORAL CARDIOTONIC AGENTS

It is estimated that 40 million Americans have diseases of the heart and blood vessels. This represents one sixth of the total population of the United States. A major consequence of these diseases is the excessive hemodynamic workload imposed on the heart. Eventually, and despite hypertrophy of its muscular wall and enlargement of its chamber (s), the heart inevitably fails. The annual incidence of cardiac failure is difficult to determine. The Pharmacological Data Service Audit, which monitored the annual consumption of digitalis, suggests that 3.5 to 4 million Americans have heart failure[44]. While this estimate includes patients receiving digitalis for the treatment and prevention of cardiac arrhythmias, it does not include patients who are receiving only diuretics for their cardiac failure. The repercussions of heart failure are cumulative, as well as individual. Patients with heart failure must bear the morbid consequences of their cardiovascular disease, almost invariably involving restrictions in lifestyle and in earning capacity. The nation, likewise, bears cumulative consequences of lost income, lowered productivity, and the burdens of the spiraling cost of medical care. To the nation's economy, this stress means a depletion of more than 50 billion dollars annually.

**Severity of Chronic Cardiac Failure and Cardiotonic Agents.** In compromising the pumping function of the heart, cardiac disease impairs oxygen delivery to the metabolizing tissues. This impairment often becomes evident only during the increased oxygen requirements attendant to exercise when cardiac output fails to rise appropriately[45,46]. Physiologically, heart failure may therefore be defined as the inabilty of the heart to maintain oxygen delivery relative to oxygen demand. This impairment in oxygen delivery can be detected during supervised progressive treadmill exercise by the noninvasive monitoring of respiratory gas exchange with the severity of cardiac failure graded according to the maximal level of oxygen uptake achieved and the onset of anaerobic metabolism[47] as indicated in Table I.

### Table I

*Grading the Severity of Chronic Cardiac Failure According to Progressive Treadmill Exercise**

| Class | Maximal Oxygen Uptake (cc/min/kg) | Onset of Anaerobic Metabolism (sec) |
|---|---|---|
| A | >20 | 540 - 600 |
| B | 16 - 20 | 420 - 480 |
| C | 10- 15 | 300 - 360 |
| D | <10 | 120 - 180 |

* Modified Naughton protocol

Patients with severe failure (exercise Class D) have little or no cardiac reserve during exercise (i.e., cardiac output rises only minimally) and a markedly restricted aerobic capacity with the early onset of anaerobic metabolism. These patients have all the clinical hallmarks of the heart failure syndrome, including orthopnea and paroxysmal nocturnal dyspnea, cardiomegaly, elevated left ventricular filling, depressed ejection fraction, and are poorly controlled by standart medical therapy. The prognosis of these patients is dismal, particularly for those with ischemic heart disease or idiopathic congestive cardiomyopathy. Of those Class D patients with idiopathic cardiomyopathy who were referred to our unit for cardionotic therapy, 70 percent were dead within 5 months, while 69 percent of those with ischemic heart disease had died within three months. Class D patients are clearly candidates for cardiotonic agents. In fact, these agents should be given to these patients much earlier in the course of their disease if there is to be any hope of precluding their progression to end-stage cardiac failure. Class C patients, while less compromised clinically, have only a modest cardiac reserve as well as cardiomegaly, elevated filling pressure and reduced ejection fraction [7]. Cardiotonic agents should also be given to these patients.

Class B patients respond to the physiologic stress of exercise in a nearly normal fashion, raising cardiac output at least three times above its resting value. Many of these patients, however, have a depressed ejection fraction and cardiomegaly. At the present time, it is uncertain whether or not the introduction of cardiotonic agents at this stage of

their disease is indicated. If the enlarged heart can be reduced in size with these agents, the course of disease may ba favorably altered.

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