Is inotropic therapy appropriate for patients with chronic congestive heart failure? Or is the digitalis leaf withering?

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Summary: The appropriateness of inotropic therapy in chronic heart failure was examined by critically reviewing five assumptions upon which this form of therapy has been justified. Only the first, that cardiac performance can be acutely improved by inotropic therapy, has been empirically proven. That such acute improvement is sustained appears to be true with non-catecholamine agents whereas the chronic haemodynamic efficacy of oral catecholamines remains in doubt. That any inotropic agent can improve exercise tolerance, make the patient feel better, or effect a change without deleteriously affecting the myocyte is very much in doubt. Thus, although the prospect of using powerful inotropic therapy in the patient with heart failure is theoretically appealing, its utility remains to be proven.

With the historical precedent of digitalis, the propriety for using an inotropic agent in chronic heart failure has, by and large, not been seriously questioned. The logic seems clear in directing therapy at the central derangement in most types of heart failure, namely myocardial dysfunction. That a positive inotropic agent can be effective therapy in chronic heart failure has not, however, been proven. The use of such agents is predicated on certain assumptions which may not be correct. These assumptions will be examined in order to consider the possible therapeutic role of inotropic therapy in chronic heart failure.

Many compounds have been shown to possess positive inotropism in isolated cardiac muscle preparations (Table I). Interestingly, most of these agents, particularly those in use or under active investigation, also demonstrate vasoactive properties. For example, the beta-1 agonist dobutamine may also produce vasodilatation by beta-2 stimulation and alpha-adrenergic antagonistic actions of its (+) isomer (Ruffolo *et al.*, 1981). It may also produce vasoconstriction by an alpha-adrenergic action of the (–) isomer (Ruffolo *et al.*, 1981). The blood pressure response is thus a summation of its multiple vasoactive

Table I A partial list of positive inotropes with a peripheral vascular action

Drug	Cardiac mechanism of action	Peripheral vascular response
Amrinone, milrinone	Phosphodiesterase inhibition	Vasodilatation
Digoxin	Inhibition of sodium-potassium ATPase pump	Vasoconstriction
Dobutamine	Beta-1 stimulation	(+) Isomer; vasodilatation (beta-2 stimulation; alpha antagonist) (–) Isomer; vasoconstriction (alpha stimulation)
Dopamine	Beta-1 stimulation	Vasodilatation of renal and mesenteric beds (low dose, dopaminergic receptor) Vasoconstriction (high dose, alpha stimulation)
MDL 17,043; MDL 19,205	Phosphodiesterase inhibition	Vasodilatation
Pirbuterol, prenalterol, salbutamol	Beta-1 stimulation	Vasodilatation (beta-2-stimulation)

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as well as its cardioactive properties (Figure 1). The digitalis compounds may produce, at least acutely, regional vasoconstriction (Mason, 1974) and the experimental inotropic agents amrinone (Ross *et al.*, 1981; van Breeman *et al.*, 1980), milrinone (Alousi *et al.*, 1983) and MDL 17,043 (Uretsky *et al.*, 1983) produce regional vasodilation.

With the caveat in mind that demonstrated effects in man may be related to the vasoactive as well as cardioactive effects of a drug, we shall examine whether certain assumptions under which these agents have been clinically used or investigated are justified.

Assumption 1 That a contractile reserve exists in patients with heart failure that may be tapped by an inotropic agent.

Multiple clinical studies have justified this assumption (Table II). Dobutamine (Leier *et al.*, 1977), dopamine (Beregovich *et al.*, 1974; Loeb *et al.*, 1971; Holzer *et al.*, 1973), amrinone (Benotti *et al.*, 1978; LeJemtel *et al.*, 1979; Maskin *et al.*, 1982), milrinone (Sinoway *et al.*, 1983; Maskin *et al.*, 1983a; Baim *et al.*, 1983), MDL 17,043 (Uretsky *et al.*, 1983), MDL 19,205 (Petain *et al.*, 1984) and ARL-115-BS (Renard *et al.*, 1983; Thormann *et al.*, 1982), among others have been shown to improve haemodynamics acutely in patients with chronic severe (New York Heart Association Class III-IV) heart failure. Such improvement may occur even with drugs that act by a beta-adrenergic mechanism which may already have been endogenously stimulated (Figure 2).

Figure 1 The individual responses of the mean arterial blood pressure (MAP) to graded infusion of intravenous dobutamine in four patients are shown.

Figure 2 The mean responses of the peak cardiac index and plasma norepinephrine level to a dobutamine infusion in nine patients are shown. The data suggest that with an improvement in cardiac performance by an exogenous sympathomimetic agent, there is a reflex decrease in endogenous sympathetic nervous system activity (as reflected by the plasma norepinephrine level).

Assumption 2 That acute haemodynamic improvement is sustained.

It is now clear that this assumption cannot be accepted without reservation. It would appear that the salutary effects of the beta-adrenergic agonists attenuate over time. Unverferth *et al.* (1980) have demon-

Table II Acute rest haemodynamic response (%) to some positive inotropic agents

Drug	Cardiac output	Left ventricular filling pressure
Amrinone		
Intravenous	+ 39 to + 50	- 23 to - 46
Oral	+ 34	- 26
Digoxin		
Oral	+ 9 to + 20	- 6 to - 38
Dobutamine		
Intravenous	+ 26 to + 69	- 11 to - 55
Dopamine		
Intravenous	+ 34 to + 70	+ 10 to - 27
MDL 17,043		
Intravenous	+ 31 to + 82	- 32 to - 48
Oral	+ 37	- 40
MDL 19,205		
Intravenous	+ 75	- 35
Milrinone		
Intravenous	+ 33 to + 53	- 33
Oral	+ 39	- 27
Pirbuterol		
Oral	+ 41 to + 50	- 17 to - 28
Prenalterol		
Oral	+ 41 to + 50	- 17 to - 38

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strated a 30% attenuation of cardiac output by 72 hours with a constant intravenous dobutamine infusion. Acute improvement in radionuclide ejection fraction with the beta agonist pirbuterol was inapparent by 4 weeks of chronic therapy (Colucci *et al.*, 1981). Three patients studied by us on chronic pirbuterol therapy had a total loss of improvement in cardiac output at 6 week restudy. It should be pointed out that certain other studies (Pamelia *et al.*, 1983; Dawson *et al.*, 1983) have suggested continued haemodynamic efficacy with this agent. The reason for these differences is not clear at this time. Lack of chronic haemodynamic effect has also been observed with the beta agonist prenalterol (Lambert *et al.*, 1984). The loss of responsivity to beta-1 agonists has been attributed to 'down regulation' of the beta-receptor, both in actual number (Colucci *et al.*, 1981; Lefkowitz *et al.*, 1984; Linden *et al.*, 1983) and effective stimulation per receptor (Lefkowitz *et al.*, 1984).

Preliminary data suggest that levodopa may be efficacious in chronically improving cardiac output through endogenous conversion of levodopa to dopamine (Rajfer *et al.*, 1984). The explanation for chronic efficacy is presently not clear but may be related to a catecholamine 'burst' effect which may improve intermittently cardiac output with short 'rest' periods for the beta receptors. Such speculation will require empiric confirmation.

Agents that work through a non-beta-adrenergic mechanism seem to maintain haemodynamic efficacy over a chronic period. These agents include digoxin (Arnold *et al.*, 1980), amrinone (Maskin *et al.*, 1982), milrinone (Maskin *et al.*, 1983a), and MDL 17,043 (Uretsky *et al.*, 1984). As opposed to the beta agonists which appear to exert their inotropic effect through the cell membrane receptor, these agents operate through other mechanisms. The digitalis compounds probably act through the cell membrane sodium-potassium ATPase pump whereas both amrinone and MDL 17,043 are potent inhibitors of cardiac phosphodiesterase which may be the major mechanism by which these agents work (Kariya *et al.* 1982). Thus, available evidence suggests that inotropic agents which work through a non-beta-adrenergic mechanism may have a sustained effectiveness in the patient with heart failure.

Assumption 3 That functional capacity can be improved.

In studies to evaluate this question, the sympathomimetic agents dobutamine and dopamine have not produced acute improvement in functional capacity (Maskin *et al.*, 1983b, 1983c; Wilson *et al.*, 1984). Neither peak workload nor exercise time has been increased with these agents. At peak exercise, cardiac output was greater than control but systemic arterial

venous oxygen difference was more narrow. These data suggest that increased cardiac output at peak exercise may be shunted to non-metabolically active tissues. This shunting may be a consequence of the peripheral vasodilation action of these drugs. Thus, we cannot state with certainty at the present time the effect on functional capacity of cardiac beta stimulation without a vasoactive component.

The ability of non-sympathomimetic agents to enhance exercise performance is also not clear at present. It may be argued that the combined inotropic effects of increased sympathetic stimulation from exercise itself plus stimulation of a second inotropic mechanism such as inhibition of the sodium-potassium ATPase pump (digitalis compounds) or phosphodiesterase inhibition (amrinone, milrinone, MDL 17,043, MDL 19,205, ARL-115-BS) would allow for greater exercise performance. Available data do not support this hypothesis. In a study by Weber *et al.* (1981), amrinone did not produce an acute improvement in exercise time and peak oxygen consumption, whereas in a study by Siskind *et al.* (1981) acute exercise performance was enhanced. Little data is presently available on acute exercise performance with other non-sympathomimetic investigational agents. Although two hundred years have elapsed since digitalis was first used for heart failure, it is unclear if this drug has any effect on acute exercise performance.

The evaluation of a drug via long-term exercise testing requires a control group and a blinding procedure. Results of exercise testing without these precautions are only convincing if exercise results show no change over the control. Under these circumstances, the drug might even be considered *detrimental* to exercise performance since a 5–20% improvement in exercise capacity over a 1–3 month follow-up period may be expected from placebo alone (Captopril Multicenter Research Group, 1983). If, on the other hand, exercise performance improves moderately (> 25%), such results should be considered encouraging but preliminary. Weber *et al.* (1981) showed a long-term improvement in a small group of patients on amrinone. Leier *et al.* (1983) in a small group showed such improvement was greater than in a control placebo group. However, in a placebo controlled multicentre, double-blind study, the improvement in exercise performance was no greater than with placebo (DiBianco *et al.*, 1983). At present, placebo-controlled, blinded studies on milrinone and MDL 17,043 currently in progress may help to clarify this issue.

Interestingly, intermittent infusions of intravenous dobutamine given in a blinded manner to ambulatory patients with heart failure have been shown to improve exercise capacity when compared to a placebo group (Leier *et al.*, 1982; Liang *et al.*, 1984). The mechanism by which such an improvement occurs is not clear at

present, although a peripheral 'drug-induced conditioning' has been suggested (Leier *et al.*, 1982).

Assumption 4 That patients with heart failure will feel better with inotropic therapy.

The evaluation of 'feeling better' is still a problem. The subjectivity on the part of the patient and investigator, and the biases towards improvement, require a control group and a blinding procedure. Nevertheless, studies without these precautions do have some value in that very low improvement rates suggest a drug will have very limited, if any, value in the treatment of heart failure whereas a drug with a very high response rate would appear worthy of a controlled trial. A second problem is related to the classification of symptoms. The New York Heart Association functional classification is discontinuous, that is, patients have to be classified as I, II, III, or IV. In order to show improvement by this scale, a patient must jump an entire class, an infrequent event in patients with severe heart failure. Using this reasoning, those who have expressed symptomatic improvement using the scale as continuous, e.g. adding a decimal to the whole number class, are probably using this classification incorrectly (Captopril Multicenter Research Group, 1983). In truth, however, we frequently consider this classification as continuous (Figure 3). In the example in Figure 3, all three patients improved to a similar degree; however, only patients 1 and 2 showed improvement using this classification. Also, the improvements in patients 1 and 2 tend to be exaggerated using this scale. Another consideration regarding symptomatic change is the time after a drug institution. Placebo effect would tend to be greatest immediately upon starting a drug. Response rates are expected to be highest on drug initiation. Therefore, the longer time a high response rate continues, the more significant it would appear to be. With these considerations, we can review existing data

Figure 3 The New York Heart Association symptom classification can be thought of as a continuous or non-continuous variable, as shown. If thought of as non-continuous in this example, patients 1 and 2 will show improvement by one class whereas patient 3 will not, although all three have improved by the same amount.

related to the ability of an inotropic agent to improve symptomatically patients with chronic heart failure.

Withering's treatise (1941) suggested that the digitalis leaf might be effective therapy for 'dropsy'. This encouraging first report has not been followed up over the past 200 years with a totally convincing controlled, randomized, blinded trial that demonstrates clearly the efficacy of digitalis in patients with heart failure and normal sinus rhythm. Withering's impression that digitalis leaf was effective therapy may have been correct but such an efficacy may have been related to control of the ventricular response in patients with atrial fibrillation. Whether an extract of the digitalis leaf or specific digitalis compounds can improve 'dropsy' independent of the effect on atrial fibrillation is still not clear. Lee *et al.* (1982) concluded, in a placebo-controlled, double-blind study, that oral digoxin improved ambulatory patients with heart failure particularly if a third heart sound was present. In a recent study by Gheorgiade & Beller (1983), in which all heart failure patients were in normal sinus rhythm, withdrawal of chronic digoxin therapy to heart failure patients, also on diuretics and in most cases, vasodilators, did not produce any detrimental effects to this group. Recently, a review of studies on digoxin's therapeutic efficacy including the methodological problems in each study has been published (Mulrow *et al.*, 1984). In summary, there is still significant controversy that any digitalis compound as a result of its inotropic action can improve symptomatically patients with congestive heart failure.

The first published reports in man on the effects of amrinone (Benotti *et al.*, 1978; LeJemtel *et al.*, 1979) occasioned tremendous enthusiasm and expectation in both the medical and lay press. Unfortunately, a large multi-centre placebo-controlled double blinded study (DiBianco *et al.*, 1983) could not demonstrate a therapeutic advantage of amrinone over placebo. It has been suggested that lack of efficacy was related to amrinone's narrow therapeutic:toxic ratio which did not allow for a high enough dose to confer a therapeutic response (Baim *et al.*, 1983). Milrinone, a congener of amrinone, is said to possess a higher therapeutic:toxic ratio. Multicentre, randomized, placebo controlled trials are now in progress with this agent as they are with another phosphodiesterase inhibitor, MDL 17,043. In summary, it may be said that at present, none of the currently investigational inotropic agents have convincingly shown the ability to symptomatically improve the patient with heart failure. Dobutamine, given as intermittent intravenous infusions over several months, has been shown to improve symptoms concomitant with improvement of functional capacity when compared to a placebo group (Leier *et al.*, 1982a; Liang *et al.*, 1984). It is unlikely that the symptomatic improvement is related only to haemodynamic changes induced by

dobutamine since patients felt better also during periods between dobutamine infusions. The mechanism by which this improvement occurs is unknown but may be related to a 'conditioning' effect in the periphery (Leier *et al.*, 1982).

Assumption 5 That the effects of an inotropic agent are not deleterious in man.

An inotropic agent may upset the tenuous balance between energy production and utilization (Katz, 1978), causing long-term deleterious effects to the individual myocardial cells. Many mundane, but clear, examples have been offered to express concerns about this form of therapy. An inotropic agent has been compared to whipping a tired horse or racing an older car. Although performance may be better for a short period for the horse or car under the above circumstances, it can be expected that such treatment will ultimately result in a shorter life span for either the car or the horse. To examine whether these analogies are representative of the effects of the inotropic drugs in man, it is worthwhile to review the effects of inotropic agents in experimental preparations and man.

One difficulty in addressing this question is the lack of an acceptable animal model of chronic heart failure. Thus, conclusions on this issue can only be drawn inferentially from acute heart failure models, and other models, both acute and chronic, of ventricular dysfunction, which may not be totally applicable to the human condition. In studies designed to produce an ischaemic myocardium, several inotropic agents including isoproterenol, norepinephrine, and dobutamine have been shown to worsen cardiac performance and to increase infarct size pathologically (Vatner *et al.*, 1974, 1976; Maroko *et al.*, 1971, 1973; Davidson *et al.*, 1974). Early studies suggested that dobutamine increased infarct size (Vatner *et al.*, 1974). In more recent studies, myocardial injury after dobutamine has either been shown not to change (Rude *et al.*, 1982) or decrease (Liang *et al.*, 1981). Discrepancies in results of early *vs* later studies have been attributed to differences in the heart rate in these studies (Liang *et al.*, 1981; Rude *et al.*, 1984). Chronic catecholamine infusions in certain animal species have produced a type of cardiomyopathy (Lee & Downing, 1982a; Yates *et al.*, 1981), although the factors producing myocardial injury have not been clarified. Unverferth *et al.* (1982) have demonstrated potentially therapeutic advantages of a 3 day infusion of dobutamine in patients with severe heart failure. Endomyocardial biopsy specimens showed an improved ATP/creatine ratio compared to pre-infusion suggesting improved health to the individual myocytes.

Is there evidence in man that inotropic therapy is deleterious? It has been suggested that *improvement* in survival be considered a therapeutic endpoint with

inotropic therapy (Braunwald & Colucci, 1984). We do not believe this finding to be necessary. Rather, we feel it is more appropriate to consider the therapeutic endpoint to be symptomatic improvement *without* a worsening in survival rate. Thus, we can raise the question of whether inotropic therapy has been shown to worsen survival, or presumably as an intermediate step, worsen long-term cardiac function. At this point, adequate long-term, placebo-controlled, blinded studies have not been performed to address those questions. As such, we can only draw inferences from existing data. As a by-product to long-term haemodynamic evaluation of various vasodilators, baseline haemodynamics at two points in time have been frequently obtained (Chatterjee *et al.*, 1980; Packer *et al.*, 1982; Leier *et al.*, 1983; Kramer *et al.*, 1983). Interestingly, most studies have shown very little difference in the baseline haemodynamics at these two points which have been taken between 12 and 37 weeks apart. Maskin *et al.* (1982), on the other hand, reported significantly worsened baseline haemodynamics after chronic (approximately 10 months) amrinone use. The authors attributed this worsening to the natural progression of the underlying cardiac disease. It is possible that the worsening may have been due to the unnatural progression related to chronic amrinone use. Recently, Packer *et al.* (1984) have demonstrated similar findings at 3 months. If amrinone, in fact, caused a deterioration in cardiac function, one might expect an increased mortality compared to that found in natural history studies. Unfortunately, such natural history studies are difficult to evaluate in that regard (Franciosa *et al.*, 1983; Wilson *et al.*, 1983). Differences in patient selection, classification of the severity of heart failure, longevity of the heart failure drug usage, and aetiology of the heart failure make comparison to an historical standard difficult. Packer *et al.* (1984) using as controls patients referred for vasodilator therapy [either hydralazine (101 patients) or captopril (70 patients)] showed a significantly lower 3-month survival rate (41%) with amrinone (29 patients) than in either control vasodilator group (65% with hydralazine, 71% with captopril). Evidence from our institution demonstrates an overall annual mortality with MDL 17,043 of at least 68%. Although our patients represent an extremely ill group on the whole, it is still unlikely, based on these figures, that MDL 17,043 improved survival and may have, in fact, worsened it (Franciosa *et al.*, 1983; Wilson *et al.*, 1983). Multicentre, controlled, randomized trials currently under way with this agent will hopefully answer this question. Finally, controversy exists even in the potential of digoxin to worsen mortality with data suggesting both a worsening (Moss *et al.*, 1981) and no effect (Ryan *et al.*, 1983) on survival. The data, although suggestive at best, emphasize the need to evaluate mortality in deciding on the propriety of

inotropic drugs in the heart failure setting.

In summary then, new inotropic therapy offers exciting potential. The available data do not, however, recommend it as a form of therapy until the above assumptions are shown to be true.

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