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Myocardial β-adrenoceptor function and regulation in heart failure: implications for therapy

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Introduction

Congestive cardiac failure (CCF) is defined as the inability of the heart to pump adequate amounts of blood to the tissues to meet their metabolic requirements. Although a wide variety of disease processes affecting both the muscular wall and valves of the heart may lead to CCF the characteristic complex of signs and symptoms are produced by a common pathophysiological pathway. This is the result of two reflex responses consequent upon the gradual loss of the heart's pump force and its inability to provide the needs of the circulation.

The first—the expansion of the circulating blood volume related to reduced renal perfusion and the activation of the renin-angiotensin-aldosterone pathway leads to the characteristic appearances of volume overload namely cardiomegaly, raised central venous pressure and peripheral and/or pulmonary oedema. The second—the over activity of the sympathetic nervous system, is an attempt to enhance the rate and force of cardiac contraction and produce varying degrees of peripheral vasoconstriction to maintain blood pressure and adequate perfusion of vital organs. These mechanisms provide sufficient support for the gradually failing heart during the development of compensated chronic CCF but may also contribute to a vicious circle of worsening disease followed by an increased reflex response with consequent overstretching and over stimulation of the heart with critical increase in myocardial oxygen demand leading finally to decompensation.

The treatment of CCF secondary to disease of the heart muscle has traditionally centred on the use of dietary sodium restriction and diuretics to control volume overload and cardiac glycosides to provide direct positive inotropic support for the failing myocardium. Although diuretics have remained a mainstay of treatment, the low therapeutic efficacy and high toxicity of digitalis has led to its replacement in many circumstances with vasodilating drugs providing indirect inotropic support via manipulation of cardiac preload and afterload (Cohn & Franciosa, 1977). There has, however, been a recent resurgence of interest in alternative approaches to direct inotropism and related to this the possible deleterious effect of chronic myocardial β-adrenoceptor over stimulation during the development of heart failure.

Mechanisms of direct inotropism: systolic and diastolic function

During the plateau phase of the cardiac action potential the concentration of free cytosolic calcium ions (Ca^{++}) in the myocyte is rapidly increased due to the influx of extracellular Ca^{++} via voltage dependent calcium channels and the release of Ca^{++} bound intracellularly to the sarcoplasmic reticulum (SR). The raised cytosolic Ca^{++} leads to increased binding of Ca^{++} to and activation of the contractile poteins. Myocardial relaxation during the recovery phase of the action potential is associated with dissociation of Ca^{++} from the contractile proteins, its reuptake into the SR and transport out of the cell via Na^+/Ca^{++} exchange mechanisms. The final common pathway of positive inotropes is the enhanced availability of free cytosolic Ca^{++} during this process. There are, however, distinct differences in the effects of different agents as is readily seen in comparing digitalis with the catecholamines (Figure 1). Thus catecholamines acting at the β-adrenoceptor increase force and rate of contraction but also the rate of myocardial relaxation leading to an overall shortening of the contractile event (Scholtz, 1980). Conversely the effect of digoxin is on force of contraction alone and the rates of both contraction and relaxation are unaffected. These differences are due to the different biochemical events following the use of the two agents. Thus digoxin enhances the availability of free cytosolic Ca^{++} as a consequence of inhibition of Na^+/K^+ ATPase which leads to increased intracellular Na^+ followed by increased

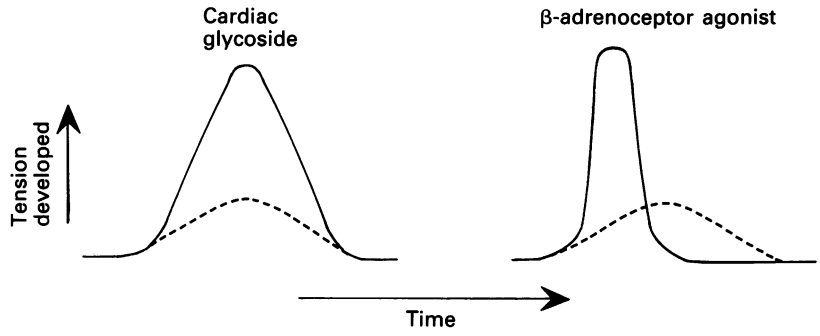

Figure 1 Diagrammatic representation of the effects of a cardiac glycoside and a β-adrenoceptor agonist on the contraction of isolated ventricular muscle. Solid line represents the effect of the agonist compared with control contraction (dotted line). Note shortening of overall contractile event with β-adrenoceptor agonist.

activity of the alternative Na^+ extrusion mechanism via Na^+/Ca^+ exchange. The paradoxical effect of catecholamines on contraction and relaxation, however, is due to cyclic AMP protein kinase mediated protein phosphorylation (Katz, 1983). This results in increased influx of Ca^{++} into the cell via voltage operated calcium channels leading to increased force of contraction, i.e. positive inotropic effect. In addition, the rate of dissociation of Ca^{++} from the contractile proteins and re-uptake into the SR is also enhanced leading to a more rapid relaxation phase, i.e. positive lusitropic effect (see Figure 2 and Legend for full explanation). These bio-chemical events are essential for the normal physiological response to β-adrenoceptor agonists. Thus activation of the sympathetic nervous system leads to increased cardiac output via increase in stroke volume and heart rate. The latter also leads to a progressive reduction of diastolic filling time as rate increases. The compensatory effect of catecholamines shortening the time of relaxation, therefore, extends the effectiveness of heart rate as a mechanism for increasing cardiac output during exercise. At very high heart rate (e.g. paroxysmal SVT) this mechanism fails and fall of cardiac output due to impaired filling occurs despite otherwise normal myocardial contractile function.

Disturbances of diastolic function in myocardial disease have long been recognised (Gaasch *et al.*, 1976) although the importance of these abnormalities and the application of specific therapy in heart failure is of more recent interest. It is intuitively obvious that if the left ventricle does not fill well during diastole then the subsequent systolic contraction will be less effective. The filling pressure or preload can be impaired by poor venous return (e.g. with dehydration) or due to loss of the atrial contraction 'booster' effect when patients change from sinus rhythm to atrial fibrillation. In addition, to these well recognised mechanisms intrinsic myocardial disease (e.g. ischaemic heart disease) leads to stiffening and loss of compliance of the left ventricle with reduced diastolic distensibility and consequently impaired filling (Bonow *et al.*, 1981). From the haemodynamic standpoint, these abnormalities of diastolic performance lead to reduced rate of LV filling, decreased contribution of atrial systole to LV filling and increased left ventricular end diastolic pressure (LVEDP). The clinical consequences are increased exertional dyspnoea and othopnoea principally due to the reduced rate of emptying of the pulmonary circulation and the loss of the normal compensatory mechanism of shortening of relaxation time during exercise induced tachycardia. In addition, inefficient filling contributes to the already impaired systolic function of the chronically diseased myocardium. Preservation of diastolic function in progressive heart failure is obviously of relevance and can be seen to be an important part of the physiological action of catecholamines. However, prolonged sympathetic nervous system over-activity in heart failure may be counter-productive and potentially harmful due to progressive loss of myocardial sensitivity to catecholamine stimulation.

Myocardial β-adrenoceptors in heart failure

It is now well established that the human heart contains a heterogeneous population of β-adrenoceptor subtypes (Hedberg *et al.*, 1985; Brodde *et al.*, 1986) in both atria and ventricles. In studies of operative specimens of human right atrial apendage it has been clearly shown that both β_1- and β_2-subtypes are coupled to adenylate

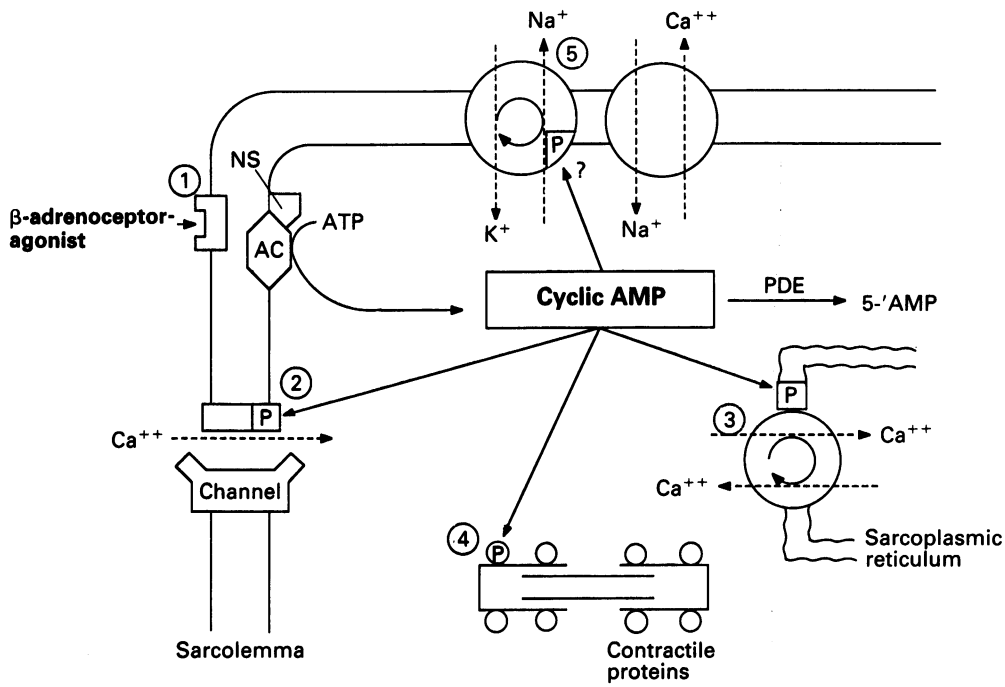

Figure 2 Cyclic AMP dependent processes effecting myocardial contraction and relaxation (inotropic and lusitropic effects).

1. β-adrenoceptor agonist stimulation of myocardial β-adrenoceptors leads to increased intracellular cyclic AMP formation. The latter activates specific protein kinase which leads to phosphorylation (P) of a variety of intracellular proteins influencing Ca^{++} transport and binding.

2. Increased transmembrane flux of Ca^{++} via voltage operated calcium channels by recruitment of 'resting' channels into the active state, leading to increased availability of free intracellular Ca^{++} and positive inotropic effects (Reuter, 1979; Tsien, 1983).

3. Increased activity of calcium ATPase pump enzyme and its sensitivity to Ca^{++} in the sarcoplasmic reticulum following phosphorylation of phospholamban (Tada & Katz, 1982). This leads to increased rate of turnover of Ca^{++} (i.e. release and storage of Ca^{++} bound) intracellularly with consequent acceleration of the rate of onset and offset of the contractile process (positive inotropic and lusitropic effects).

4. Phosphorylation of specific contractile proteins in particular troponin I (Katz, 1979). This protein participates in an allosteric response in which Ca^{++} binding regulates the interaction of actin and myosin: Phosphorylation desensitises the contractile proteins to Ca^{++} and increases its rate of dissociation from specific binding sites, leading to enhanced rate of relaxation (positive lusitropic effect).

5. ?Na^+ pump stimulation by possible increased activity of cell membrane Na^+/K^+ ATPase (Morad, 1982). Resulting stimulation of Na^+ extrusion from the cell leads to increased transmembrane Na^+ gradient and acceleration of Ca^{++} efflux via Na^+:Ca^{++} exchange mechanism (positive lusitropic effect).

cyclase and linked mechanically to the inotropic response of the atria (Ask *et al.*, 1985). Co-existence of subtypes has also been established in human ventricles using normal human heart (Bristow *et al.*, 1986). In these experiments hearts were obtained from 'would be' donors who had suffered traumatic brain death and were not used for transplantation because of late developing complications in the recipient, unsuitable match or insurmountable technical problems. Both β_1- and β_2-adrenoceptors were identified by radioligand binding in right and left ventricles in a ratio of approximately 75/25. In addition in tissue bath experiments these workers compared the effects of non-selective and subtype selective β-adrenoceptor agonists on the contractile responses of isolated ventricular muscle. The results suggested that maximal inotropic response is divided between β_1- and β_2-adrenoceptors in a similar proportion to that found in the binding studies.

In cardiac failure, plasma noradrenaline levels are increased reflecting activation of the sympathetic nervous system (Thomas & Marks, 1978). Levels are considerably higher in patients with the more severe symptoms indicating a

close relationship between increasing cardiac decompensation and the level of plasma noradrenaline. The degree of this correlation is sufficient for a number of authors to have suggested that resting plasma noradrenaline provides a better prognostic indicator of disease severity in heart failure than other measures of cardiac performance (Cohn *et al.*, 1984). Almost certainly as a consequence of the increased sympathetic nervous activity and high circulating catecholamines cardiac failure is associated with major alteration in myocardial β-adrenoceptor density. A number of reports have demonstrated reduced density of β-adrenoceptors, using ligand binding, in ventricular muscle obtained from heart transplant recipients in severe cardiac failure. The 'down regulation' of β-adrenoceptors was correlated with reduced contractile response of muscle strips, and cyclic AMP generation to β-adrenoceptor agonists. This effect is receptor specific as no change in response to histamine acting on myocardial H_2-receptors coupled to adenylate cyclase was found in the same tissue (Bristow *et al.*, 1982). Two recent studies have extended these observations. In the first Fowler *et al.* (1986) addressed the hypothesis that β-adrenoceptor down regulation may simply be an incidental finding in end stage disease. They examined β-adrenoceptor density in endomyocardial biopsies from the right ventricle of normal controls and patients at various stages of cardiac failure. Despite the technical difficulties involved these workers established a close correlation between receptor down regulation and the degree of cardiac impairment as measured by left ventricular ejection fraction (LVEF). Thus total β-adrenoceptor density was reduced by 58% in severe failure (LVEF < 0.25) and by only 38% in subjects less affected (LVEF between 0.5 and 0.25). In addition some subjects in each group were given graded sequential infusions of dobutamine (β-adrenoceptor stimulation—see later) and calcium gluconate (representing maximum inotropism) to assess *in vivo* inotropic response. The proportional reduction of dobutamine response compared with the effect of the calcium infusion correlated well with both the decrease in LVEF and reduction of β-adrenoceptor density. Although, it is uncertain whether changes seen in right ventricular endomyocardial biopsies are representative of the whole heart, these studies go some way to confirming the possible pathophysiological relationship between progressive cardiac failure and reduced β-adrenoceptor density and function.

In the second study using larger fragments of ventricular muscle from transplant recipients Bristow *et al.* (1986) examined the relative proportions of β-adrenoceptor subtypes. They found that the ratio of β_1- and β_2-adrenoceptors in severely failing hearts (60/40) was markedly different from normal controls (75/25 see above) This was due to a proportionately greater down regulation of the β_1-adrenoceptor with relative sparing of the β_2-subtype. As with the other half of this study in normal hearts, previously referred to, these experiments were extended to include the inotropic response of ventricular muscle strips to non-selective and selective β-adrenoceptor agonists. The findings of relative preservation of β_2-adrenoceptors in severe heart failure were mirrored exactly in the *in vitro* functional experiments.

It has been proposed that myocardial β_2-adrenoceptors are situated extra-junctionally and are non-innervated 'hormonal' receptors responding principally to circulating adrenaline whereas the post synaptic β_1-adrenoceptors are closely associated with the noradrenergic nerve terminal and neuronally released noradrenaline (Ariens, 1981). The observations of Bristow *et al.* (1986) are consistent with myocardial β_1-adrenoceptors receiving the major direct effects of increased activity of noradrenergic innervation in heart failure leading to selective down regulation and relative β_2-adrenoceptor sparing. A possible corollary of these observations is that during the development of heart failure the β_2-adrenoceptor subpopulation becomes an increasingly more important mediator of inotropic response to catecholamines or therapeutically administered β_2-adrenoceptor agonists. Conversely it may be that the loss of β_1-adrenoceptor response to sympathetic nervous stimulation is an important part of the pathophysiology of cardiac decompensation and that preservation of this pathway may influence the progression of cardiac failure. Finally extrapolation of these findings in 'end stage' heart failure to lesser forms of the disease may be inappropriate. Thus studies of short term infusions (up to 72 h) of the full agonist isoprenaline to rats have shown a selective and rapid down regulation of β_2-adrenoceptors whilst β_1-adrenoceptors are more slowly affected (Lu & Barnett, 1988). These results might more closely represent the 'physiological' regulation of myocardial β-adrenoceptors during early compensated heart failure.

Therapeutic implications

From the foregoing it can be seen that declining diastolic performance and β-adrenoceptor function are probably important pathogenetic mechanisms in progressive heart failure. What

available therapeutic strategies could influence either or both of these mechanisms?

β-adrenoceptor blockade

Traditionally β-adrenoceptor blockers have been contra-indicated in cardiac failure because of their negative inotropic action, exacerbated in the situation of high 'sympathetic drive' found in this condition. However, a number of largely uncontrolled studies in small numbers of patients has suggested a beneficial effect on mortality in patients treated with carefully titrated doses of β-adrenoceptor blockers added to existing therapy for cardiac failure. In one study 28 patients with severe congestive cardiomyopathy, without evidence of coronary artery disease, were treated with β-adrenoceptor blockers (practolol, alprenolol or metoprolol) in addition to their usual therapy of diuretics and digoxin for 6 to 62 months (Swedberg *et al.*, 1980a). Measurements non-invasively (echocardiography) of systolic and diastolic function were made as well as assessment of symptoms and physical capacity where possible. The echocardiographic findings indicated an improvement in both systolic and diastolic function with overall ejection fraction increased by approximately 30%. Most patients improved functionally and in a few this was quite dramatic. During follow up 10 patients died and this was considered by the authors to be a lower mortality than might have been expected when compared retrospectively with a similar group not given β-adrenoceptor blockers. Fifteen of the patients who had shown 'conspicuous' improvement were further studied after withdrawal of β-adrenoceptor blockers (Swedberg *et al.*, 1980b). In this group there was significant worsening in objective haemodynamic measurements and symptoms which was reversed after reinstitution of therapy although this sometimes took several months. A more recent study evaluated β-adrenoceptor blockade with metoprolol compared with placebo added to standard therapy using a randomised parallel group design in 50 patients (Anderson *et al.*, 1985). All patients had heart failure (NYHA grade II-IV) and low ejection fractions but were overall not as 'sick' as those studied by Swedberg *et al.* (1980). The results indicated that there was a trend towards improved functional class and better prognosis in the metoprolol group but no significant difference in overall mortality between groups during the follow up period (up to 19 months) was found. These less impressive results may have been due to the small group size and the generally less severe heart failure studied.

Although response is variable, clearly some patients benefit dramatically from β-adrenoceptor blockade albeit after several weeks or months of treatment. Slowing of possibly metabolically wasteful, resting tachycardia and protection from the 'cardiotoxic' effects of high levels of circulating catecholamines have been hypotheses put forward to explain the improvements seen. In addition the use of a β-adrenoceptor antagonist may prevent progressive down regulation of the cardiac β-adrenoceptor or induce recovery and up regulation. This latter effect has been demonstrated in animals (Aarons & Molinoff, 1982) and more recently in man during chronic β-adrenoceptor blocker treatment. Thus Golf & Hansson (1986) studied atrial biopsy specimens from patients coming to coronary bypass surgery and showed them to contain 17% fewer β-adrenoceptors in patients not previously taking β-adrenoceptor blockers compared with those who had been. Partial agonist activity of the β-adrenoceptor blocker appeared to enhance the degree of relative up-regulation. In those patients who had been pre-treated with pindolol, β-adrenoceptor density was 51% higher than non-treated subjects compared with 38% higher in patients receiving β-adrenoceptor blockers without partial agonist activity, all these differences were highly significant. In addition the relative proportions of β_1- and β_2 subtypes were similar in treated and non-treated groups and was not affected by the use of β_1-selective *vs* non-selective β-adrenoceptor blockers. However, it is difficult to envisage what use these 'revitalised' β-adrenoceptors are if they remain blocked by continued presence of the antagonist.

At present these observations of the effects of β-adrenoceptor blocker therapy have not been translated into widespread clinical practice and their use in chronic heart failure remains experimental. The action of partial agonists may be of importance and is considered later.

β-adrenoceptor agonists

For many years attempts have been made to use catecholamines in various forms to provide inotropic support for the failing heart. Lack of selectivity of action leads to combination effects on the cardiovascular system not all of which (e.g. tachycardia and vasoconstriction) are beneficial. In addition chronic agonist stimulation may further exacerbate down regulation of myocardial β-adrenoceptors, increase cardiac oxygen demand and contribute to the progression of myocardial disease.

A number of agents are available which act

Table 1 Inotropic agents in heart failure*

	Direct effects on myocardium				*Peripheral vasculature*	
	Contraction	*Relaxation*	*Blood pressure*	*Heart rate*	*Arteries*	*Veins*
Digoxin	↑ ++	0	0	↓ (particularly in AF)	? dilate	0
Dopamine	↑ +	↑ +	↑ ↓	↑ + to ++	dilate renal constrict general	0
Dobutamine	↑ +++	↑ ++	↑ ↓	0 to +	dilate +	0
Pirbuterol	↑ +	↑ +	↑ ↓	↑ + to ++	dilate ++	dilate +
Xamoterol	↑ + to ++	↑ + to ++	0	0 (at rest) ↓ (exercise)	0	0
PDE inhibitors	↑ +	↑ + or ↓	↑ ↓	↑ +	dilate ++	dilate +

* Only relative qualitative effects are indicated for general comparison between the agents.
↑ represents increase; ↓ represents decrease; ↑ ↓ represents variable effect; 0 represents no effect.

directly or indirectly via stimulation of cardiac β-adrenoceptors. The variety of drugs potentially of use includes full and partial agonists, subtype selective agents and drugs with additional actions on other receptors and on the systemic vasculature. The more important of these will be briefly considered with particular reference to their use in chronic heart failure. The principal effects of these agents are also compared in Table 1.

Dopamine

Dopamine as an intravenous agent has been extensively used to provide inotropic support in various clinical situations including acute myocardial infarction. Its beneficial haemodynamic effects can be attributed to inotropic action at cardiac β-adrenoceptors via enhancement of noradrenaline release as well as agonist activity at dopamine receptors in the peripheral vasculature. At low doses this latter effect beneficially induces renal arterial vasodilation but higher doses lead to generalised vasoconstriction due to increased noradrenaline effects on vascular α_1-adrenoceptors. Its lack of 'selectivity' for stimulation of β_1- and β_2-adrenoceptors may account for the troublesome and unwanted tachycardia often seen during its use. Although dopamine can only be administered intravenously several parenteral formulations have been evaluated. L-dopa (converted to dopamine after oral ingestion) administered to a small group of patients in severe cardiac failure in addition to their usual therapy has been shown to produce acute haemodynamic response similar in quality to i.v. dopamine and a modest sustained improvement in cardiac function up to 12 months (Raijfer *et al.*, 1984). These effects were correlated with the generation in the plasma of substantial amounts of dopamine. Other orally active agents which have produced beneficial haemodynamic effects in heart failure include propylbutyl dopamine and ibopamine which is converted to *N*-methyl dopamine after oral ingestion (Fennell *et al.*, 1983; Dei Cas *et al.*, 1983). As with L-dopa the relative roles of positive inotropic action and peripheral vasodilatation in the beneficial effects of these drugs is uncertain. Although not formally evaluated dopamine would be expected to improve diastolic as well as systolic function but this would also be influenced by its peripheral effects. It is not known whether chronic therapy will adversely influence β-adrenoceptor down regulation. In view of the complex actions of this agent and the potentially deleterious effects of induced tachycardia and peripheral vasoconstriction routine use of L-dopa or other dopamine analogues in chronic heart failure cannot be recommended at present.

Dobutamine

Dobutamine is a synthetic sympathomimetic agent with variable action at β_1-, β_2-, α_1- and α_2-adrenoceptors. It is a racemic mixture and the (−)-isomer is predominantly a potent α_1-adrenoceptor agonist whilst the (+)-isomer is responsible for the actions of the drug at β_1- and β_2-adrenoceptors (Ruffolo, 1987). A number of studies suggest the presence of α_1-adrenoceptors in human heart mediating some inotropic but not chronotropic effects of noradrenaline (Bruckner *et al.*, 1984). Consequently the inotropic action of dobutamine probably results from a combined β_1- and α_1-adrenoceptor stimulation and this could in part explain the inotropic *vs* chronotropic selectivity of the compound. It is of interest that the α_1 mediated

effect on the myocardium is not associated with generation of cyclic AMP and leads predominantly to increased force of contraction with no effect on myocardial relaxation (Endoh, 1986). The overall result of dobutamine's action on cardiac diastolic function is, therefore, unpredictable. In the vasculature β_2-adrenoceptor mediated vasodilatory effects of dobutamine are partly offset by α_1-adrenoceptor mediated vasoconstriction such that changes in blood pressure and afterload are minimal. During infusion of this drug, however, net vascular resistance is reduced probably as a result of increased cardiac output and withdrawal of excess sympathetic tone. Dobutamine can only be given intravenously and is principally of use in acute situations. Recently, however, there has been much interest in the use of repetitive short term (48–72 h) infusions in patients with severe cardiac failure (Unverferth *et al.*, 1980a). The effectiveness of dobutamine used in this way is prolonged for up to 4–10 weeks after the end of the infusion. Although no effect on survival rates has been seen, clinically useful improvement in functional status of patients in intractable failure has been demonstrated (Liang *et al.*, 1984). The possibility of chronic ambulatory use of repetitive dobutamine infusions has been explored by several workers and this therapy may help to maintain individuals in terminal failure awaiting cardiac transplantation (Hodgson *et al.*, 1984).

The effects of chronic dobutamine therapy on β-adrenoceptor density have not been studied. However, in rats exposed to long term infusion of isoprenaline, leading to β-adrenoceptor down regulation, dobutamine is still able to produce a measurable inotropic response although that to isoprenaline is significantly reduced (Hayes *et al.*, 1985). The dobutamine effect in this animal model is blocked by α-adrenoceptor antagonists possibly indicating that α_1 mediated inotropism may be more important in the action of this drug in chronic heart failure. However, tolerance to the effects of dobutamine does occur during chronic use, such that approximately half the initial haemodynamic response to a given serum concentration of the drug is lost after a 3–4 day infusion (Unverferth *et al.*, 1980b).

β-adrenoceptor partial agonists

The use of β-adrenoceptor partial agonists in chronic heart failure may be beneficial, theoretically combining the advantages of β-adrenoceptor blockade, i.e. protection from catecholamine 'toxicity' and receptor down regulation (see above) with maintenance of modest inotropic and lusitropic support. The use of partial agonists is, however, not without its pitfalls. Compared with full agonists, partial agonists require occupation of a larger proportion of total available receptors to initiate a given response. Consequently a reduction in the number of myocardial β-adrenoceptors due to down regulation (as in heart failure) causes a greater reduction in response to a partial compared with a full agonist (Ruffolo, 1982). Thus using the model of myocardial β-adrenoceptor down regulation following chronic isoprenaline infusion in rats, Kenakin & Ferris (1983) showed that the inotropic response to isoprenaline was reduced by 10 fold in treated animals, whereas that to partial agonists (prenalterol, pirbuterol—see later) was completely abolished. How do these apparently paradoxical effects work out in practice?

i) β_2-adrenoceptor partial agonists

β_2-adrenoceptor stimulation could provide an ideal approach to treatment of heart failure, combining direct inotropic and lusitropic effects (Sharma & Goodwin, 1978) with peripheral vasodilation and afterload reduction. In addition, the evidence previously cited from hearts of transplant recipients (Bristow *et al.*, 1986) suggests relative protection of the myocardial β_2-adrenoceptors from down regulation in severe heart failure making them a suitable target for selective agonists. In practice β_2-adrenoceptor agonists have not been successful for chronic heart failure treatment. Thus Colucci *et al.* (1981) have shown that the initial positive inotropic effect of the β_2-adrenoceptor agonist pirbuterol was lost 4 to 7 days after commencement of treatment in patients with moderate to severe heart failure (NYHA Class III-IV). This 'tachyphylaxis' of response was associated with down regulation of β_2-adrenoceptors assessed by radioligand binding on peripheral lymphocytes in these patients over a similar time course. Long term use of β_2-adrenoceptor agonists in heart failure is, therefore, not recommended. Short term infusions of these agents may be of some benefit in the acute situation (Sharma & Goodwin, 1978) producing vasodilatation and afterload reduction. Their use has, however, been complicated by excessive tachycardia and provides no additional benefit over the other parenteral agents available.

ii) β_1-adrenoceptor partial agonists

Two agents in this class have been studied clinically. Prenalterol, a partial agonist with up to

70% of the agonist activity of isoprenaline in some tissues is relatively poorly selective for β_1-adrenoceptors (Apperley *et al.*, 1982; Mattson *et al.*, 1982). In both functional and radioligand binding experiments (Cook *et al.*, 1984) it has mixed effects on both β_1- and β_2-subtypes although the degree to which these heterogeneous effects can be demonstrated is tissue dependent (Mattson *et al.*, 1982). Following a short career in clinical use prenalterol has been withdrawn because of potential toxicity problems. In addition early trials indicated tachyphylaxis to the initial positive inotropic response after one or two months therapy in heart failure patients (Waagstein *et al.*, 1981) despite evidence in animals of lack of down regulation of β-adrenoceptors during chronic treatment (Hedberg *et al.*, 1984).

More recently xamoterol, a β_1-adrenoceptor partial agonist with approximately 43% of the agonist activity of isoprenaline (Nuttall & Snow, 1982) has become available and is now licensed for use in mild to moderate heart failure. Xamoterol is more β_1-selective than prenalterol (Cook *et al.*, 1984) and in animal studies exhibits no peripheral vasodilating effects in doses producing significant positive inotropism (Nuttall & Snow, 1982). In normal volunteers and heart failure patients it has a 'stabilising' action on sympathetic drive producing little or no effect on resting heart rate whilst inhibiting rapid exercise induced tachycardia (Hashimoto *et al.*, 1986; Sato *et al.*, 1987). Xamoterol has positive inotropic effects in normal volunteers (Hashimoto *et al.*, 1986) and positive inotropic and lusitropic effects have been demonstrated in patients with ischaemic heart failure (Pouleur *et al.*, 1982, 1986). In a similar group of patients acute intravenous administration of xamoterol did not modify myocardial oxygen consumption or lactate extraction despite a positive inotropic effect (Rousseau *et al.*, 1983). This apparent paradox may be due to the balanced effect of the drug on myocardial relaxation with overall improved efficiency of cardiac contraction. Tachyphylaxis during chronic usage appears not to be a problem with this agent (Rousseau & Pouleur, 1983). In addition there is no evidence of myocardial β-adrenoceptor down regulation in rats chronically infused (up to 6 days) with xamoterol compared with the significant loss of receptors with isoprenaline in the same model (Barnett & Maguire, 1986).

Results so far for xamoterol treatment of chronic mild to moderate heart failure in double-blind comparison with placebo and digoxin are encouraging, with patients continuing to respond for 3 months or more (The German and Austrian Xamoterol Study Group, 1988). Initial optimism with this agent, however, must be tinged with caution. By the nature of its partial agonism xamoterol will have β-adrenoceptor blocking effects in situations of high sympathetic drive and may worsen severe heart failure (NYHA Grade IV) in which it is presently contra-indicated (Bhatia & Swedberg, 1986).

In theory long term use of a β_1-adrenoceptor partial agonist would be associated with recovery of previously down regulated myocardial β_1-adrenoceptors although this aspect of chronic xamoterol therapy has not yet been studied. It is too early to say whether long term use of drugs in this class and potential receptor up regulation will be associated with slowing of progression or improved mortality in heart failure, but this will obviously be an important area for future evaluation.

Cyclic AMP phosphodiesterase inhibitors

Phosphodiesterase (PDE) inhibitors will mimic in some respects the effects of β-adrenoceptor stimulation by increasing, via an alternative pathway intracellular cyclic AMP and are, therefore briefly considered here for comparison.

Theophylline has for many years been used as a positive inotrope/weak diuretic in acute heart failure. Its cardiac effects may be as much due to its action as an antagonist for the receptor for the negatively inotropic neurotransmitter adenosine, as to PDE inhibition (Persson *et al.*, 1983). Recent data, however, suggests that selective inhibition of PDE enzyme F-III which is relatively specific for cyclic AMP is more closely correlated with the inotropic action of the newer agents, e.g. amrinone and milrinone than to effects on adrenosine receptors (Kariya *et al.*, 1982). The action of PDE inhibitors on intracellular cyclic AMP are not tissue selective and, therefore, significant vasodilatation can be expected with these drugs. In heart failure intravenous or oral amrinone produces marked increase in cardiac output with lowering of left ventricular filling pressure and reduction in systemic vascular resistance (LeJemtel *et al.*, 1979). The relative contributions of after load reduction and increased contractility to the haemodynamic improvements seen are controversial. Some investigators find no evidence of direct positive inotropism in patients with heart failure and ascribe amrinone's effects entirely to its vasodilatory properties (Firth *et al.*, 1984). The overall effects are probably a combination of the two with relative contributions of inotropism and vasodilation being dependent on dosage and the patient's

physiological state. The use of amrinone is associated with significant toxicity including gastrointestinal upset, thrombocytopenia and liver disturbances. In addition although initial improvement during open study of chronic oral therapy has been maintained over 28 weeks (Likoff *et al.*, 1984), long term beneficial effects remain unproven in controlled trials (Massie *et al.*, 1985).

Milrinone is 15 times more potent than amrinone on a per milligram basis and has similar pharmacological and haemodynamic effects (Colucci *et al.*, 1986). In severe heart failure milrinone causes no increase in myocardial oxygen consumption almost certainly related to the balanced effects of direct inotropism and vasodilation producing a reduction of LVEDP and ventricular wall stress (Morad *et al.*, 1985). Milrinone is better tolerated than amrinone although in some patients exacerbation of ventricular arrhythmias at high doses has been reported. Present evidence suggests that improvements in patients with heart failure during long term oral therapy are maintained with milrinone but no definite effect on patient survival or progression of disease has yet been demonstrated (Colucci *et al.*, 1986). None of the newer PDE inhibitors is presently licensed for general use in the UK.

Finally chronic PDE inhibition and increased intracellular cyclic AMP levels may lead to heterologous desensitisation of β-adrenoceptor responsiveness in cardiac cells by an action on guanine nucleotide binding proteins and coupling to adenylate cyclase (Bobik & Little, 1984). The consequences of this effect in heart failure management can only be speculative, but in view of previous discussion could exacerbate the progressive catecholamine induced myocardial β-adrenoceptor down regulation.

Conclusions

Ever since the development of our understanding of digoxin's effect as a positive inotrope, alternative agents to directly stimulate myocardial contractility have been sought. In recent years this approach has been overshadowed by the major advances in vasodilator therapy for heart failure with significant improvement in patients' symptoms and, probably with the ACE inhibitors, long term prognosis (Consensus Trial Study Group, 1987). However, a number of drugs are now available which interact either directly or indirectly with myocardial β-adrenoceptors with important effects on myocardial efficiency (inotropic and lusitropic action) and receptor regulation. Most of these agents have mixed and occasionally unpredictable effects on the heart and peripheral circulation and only some are available in oral dosage form. As a pure cardioactive drug xamoterol at present seems the most interesting although experience in clinical practice will determine whether this initial promise is borne out in the longer term. Newer derivatives on the theme of dopamine analogues, PDE inhibition and agents that increase the Ca^{++} sensitivity of the contractile proteins are on the horizon and will be investigated enthusiastically by clinical scientists (Wetzel & Haver, 1988). However, the bottom line for efficacy will remain slowing of disease progression and patient survival. In this regard all of the agents discussed in this review will have to be compared with ACE inhibition as the present 'gold standard'.

References

Aarons, R. D. & Molinoff, P. B. (1982). Changes in density of beta adrenergic receptors in rat lymphocytes, heart and lung after chronic treatment with propranolol. *J. Pharmac. exp. Ther.*, **221**, 439–443.

Anderson, J. L., Lutz, J. R., Gilbert, E. M., Sorensen, S. G. (1985). A randomised trial of low dose beta blockade therapy for idiopathic cardiomyopathy. *Am. J. Cardiol.*, **55**, 471–475.

Apperley, G. H., Drew, G. M. & Sullivan, A. J. (1982). Prenalterol is an agonist at $beta_2$ as well as at $beta_1$ adrenoceptors. *Eur. J. Pharmac.*, **81**, 659–663.

Ariens, E. J. (1981). The classification of beta adrenoceptors. *Trends pharmac. Sci.*, **2**, 170–172.

Ask, J. A., Stene-Larsen, G., Helle, K. B. & Resch, F. (1985). Functional $beta_1$ and $beta_2$ adrenoceptors in the human myocardium. *Acta Physiol. Scand.*, **123**, 81–88.

Barnett, D. B. & Maguire, M. (1986). Comparison of the effects of xamoterol and isoprenaline on rat ventricular beta adrenoceptors. *Br. J. Pharmac.*, **81**, 223P.

Bhatia, S. J. S. & Swedberg, K. (1986). Acute haemodynamic and metabolic effects of ICI 118587: A selective partial $beta_1$ agonist in patients with dilated cardiomyopathy. *Am. Heart J.*, **111**, 692–696.

Bobik, A. & Little, P. J. (1984). Role of cyclic AMP in cardiac beta adrenoceptor desensitisation: Studies using prenalterol and inhibitors of phosphodiesterase. *J. cardiovasc. Pharmac.*, **6**, 795–801.

Bonow, R. O., Bacharach, S. L. & Green, M. V. (1981). Impaired left ventricular diastolic filling in patients with coronary artery disease. Assessment with radionucleide cineangiography. *Circulation*, **64**, 315–323.

Bristow, M. R., Ginsberg, R., Minobe, W., Cubiciotti, R. S., Scott-Sageman, W., Lurie, R., Billingham, M. E., Harrison, D. C. & Stinson, E. B. (1982).

Decreased catecholamine sensitivity and beta adrenergic receptor density in failing human hearts. *New Engl. J. Med.*, **307**, 205–211.

Bristow, M. R., Ginsberg, R., Umans, V., Fowler, M., Minobe, W., Rasmussen, R., Zera, P., Menlove, R., Shah, P., Jamieson, S. & Stinson, E. B. (1986). Beta$_1$ and beta$_2$ adrenergic receptor subpopulations in non failing and failing human ventricular myocardium: Coupling of both receptor subtypes to muscle contraction and selective beta$_1$ receptor down regulation in heart failure. *Circulation Res.*, **59**, 297–309.

Brodde, O. E., Schuler, S., Kreisch, R., Brinkman, M., Borst, H. G., Hetzer, R., Reidemeister, J. C., Warnecke, H. & Zerkowski, H-R. (1986). Regional distribution of beta adrenoceptors in the human heart: Co-existence of functional beta$_1$ and beta$_2$ adrenoceptors in both atria and ventricles in severe congestive cardiomyopathy. *J. cardiovasc. Pharmac.*, **8**, 1235–1242.

Bruckner, R., Meyer, W., Mugge, A., Schmitz, W. & Scholz, H. (1984). Alpha adrenoceptor mediated positive inotropic effect of phenylephrine in isolated human ventricular myocardium. *Eur. J. Pharmac.*, **99**, 345–347.

Cohn, J. N. & Franciosa, J. A. (1977). Vasodilator therapy of cardiac failure. *New Engl. J. Med.*, **297**, 27–31, 254–258.

Cohn, J. N., Levine, B., Olivari, M. T., Garberg, V., Lura, D., Francis, G. S., Simon, A. B. & Rector, T. (1984). Plasma norepinephrine as a guide to prognosis in patients with chronic congestive cardiac failure. *New Engl. J. Med.*, **311**, 819–823.

Colucci, W. S., Alexander, R. W., Williams, G. H., Rude, R. E., Holman, L., Konstam, M. A., Wynn, J., Mudge, G. H. & Braunwald, E. (1981). Decreased lymphocyte beta adrenergic receptor density in patients with heart failure and tolerance to the beta adrenergic agonist pirbuterol. *New Engl. J. Med.*, **305**, 185–190.

Colucci, W. S., Wright, R. & Braunwald, E. (1986). New positive inotropic agents in the treatment of heart failure: mechanisms of action and recent clinical developments. *New Engl. J. Med.*, **314**, 290–299, 349–358.

Consensus Trial Study Group (1987). Effects of enalapril on mortality in severe congestive heart failure: Results of the co-operative North Scandinavian Enalapril Survival Study. *New Engl. J. Med.*, **316**, 1429–1435.

Cook, N., Richardson, A. & Barnett, D. B., (1984). Comparison of the beta$_1$ selective affinity of prenalterol and corwin demonstrated by radioligand binding. *Eur. J. Pharmac.*, **98**, 407–412.

Dei Cas, L., Bolognesi, R., Cucchini, F. & Fappani, A. (1983). Haemodynamic effects of ibopamine in patients with idiopathic congestive cardiomyopathy. *J. cardiovasc. Pharmac.*, **5**, 249–253.

Endoh, M. (1986). Regulation of myocardial contractility via adrenoceptors: Differential mechanisms of alpha and beta adrenoceptor mediated actions. In *New aspects of the role of adrenoceptors in the cardiovascular system*, ed. Grobecker, 78–105. Berlin: Springer Verlag.

Fennell, W. H., Taylor, A. A., Young, J. B., Brandon, T. A., Ginos, J. Z., Goldberg, M. D. & Mitchell, J. R. (1983). Propylbutyl dopamine: Haemodynamic effects in conscious dogs, normal human volunteers and patients with heart failure. *Circulation*, **67**, 829–836.

Firth, B., Ratner, A. V., Grassman, E. D., Winnifred, M. D., Nicod, P. & Hillis, L. D. (1984). Assessment of the inotropic and vasodilator effects of amrinone versus isoproterenol. *Am. J. Cardiol.*, **54**, 1331–1336.

Fowler, M. B., Laser, J. A., Hopkins, G. L., Minobe, W. & Bristow, M. R. (1986). Assessment of the beta adrenergic pathway in the intact failing human heart: Progressive receptor down regulation and subsensitivity to agonist response. *Circulation*, **74**, 1290–1302.

Gaasch, W. H., Levine, H. J., Quinones, M. A. & Alexander, J. K. (1976). Left ventricular compliance: Mechanisms and clinical implications. *Am. J. Cardiol.*, **38**, 645–652.

The German and Austrian Xamoterol Study Group (1988). Double-blind placebo controlled comparison of digoxin and xamoterol in chronic heart failure. *Lancet*, **i**, 489–493.

Golf, S. & Hansson, V. (1986). Effects of beta blocking agents on the density of beta adrenoceptors and adenylate cyclase response in human myocardium: intrinsic sympathomimetic activity favours receptor up regulation. *Cardiovasc. Res.*, **20**, 637–644.

Hashimoto, T., Shiina, A., Toyo-Oka, T., Hosoda, S. & Kondo, K. (1986). The cardiovascular effects of xamoterol, a beta$_1$ adrenoceptor partial agonist in healthy volunteers at rest. *Br. J. clin. Pharmac.*, **21**, 259–265.

Hayes, J. S., Bololing, N. & Pollock, G. D. (1985). Effects of beta adrenoceptor down regulation on the cardiovascular responses to the enantiomers of dobutamine. *J. Pharmac. exp. Ther.*, **235**, 58–65.

Hedberg, A., Kemp, K. F., Josephson, M. E. & Molinoff, P. B. (1985). Co-existence of beta$_1$ and beta$_2$ adrenergic receptors in the human heart: effects of treatment with receptor antagonists or calcium entry blockers. *J. Pharmac. exp. Ther.*, **212**, 503–508.

Hedberg, A., Mattson, H., Nerme, V. & Carlsson, E. (1984). Effects of in vivo treatment with isoprenaline or prenalterol on beta adrenoceptor mechanisms in the heart and soleous muscle of the cat. *Naunyn Schmiedberg's Arch. Pharmac.*, **325**, 251–258.

Hodgson, J. M., Aja, M. & Sorkin, R. P. (1984). Intermittent ambulatory dobutamine infusions for patients awaiting cardiac transplantation. *Am. J. Cardiol.*, **53**, 375–376.

Kariya, T., Wille, L. J. & Dage, R. C. (1982). Biochemical studies on the mechanisms of cardiotonic activity of MDL 17,043. *J. cardiovasc. Pharmac.*, **4**, 509–514.

Katz, A. M. (1979). Role of contractile proteins and sarcoplasmic reticulum in the response of the heart to catecholamines: an historical review. *Adv. Cyclic Nucl. Res.*, **11**, 303–343.

Katz, A. M. (1983). Cyclic adenosine monophosphate effects on the myocardium: A man who blows hot and cold with one breath. *J. Am. Coll. Cardiol.*, **2**, 143–149.

Kenakin, T. P. & Ferris, R. M. (1983). Effects of in vivo beta adrenoceptor down regulation on cardiac responses to prenalterol and pirbuterol. *J. cardiovasc. Pharmac.*, **5**, 90–97.

Ledda, F., Marchetti, P. & Mugeki, A. (1978). Studies on the positive inotropic effect of phenylephrine: A comparison with isoprenaline. *Br. J. Pharmac.*, **54**, 83–90.

LeJemtel, T. H., Keung, E., Sonnenblick, E. H. *et al.* (1979). Amrinone: A new non glycosidic, non adrenergic, cardiotonic effective in the treatment of intractable myocardial failure in man. *Circulation*, **59**, 1098–1104.

Liang, C., Sherman, L. G., Doherty, J. U., Wellington, K., Lee, V. W. & Hood, W. B. (1984). Sustained improvement in cardiac function in patients with congestive heart failure after short term infusion of dobutamine. *Circulation*, **69**, 113–119.

Likoff, M. J., Weber, K. T., Andrews, V. *et al.* (1984). Amrinone in the treatment of chronic cardiac failure. *J. Am. Coll. Cardiol.*, **3**, 1282–1290.

Lu, X. & Barnett, D. B. (1988). Differential regulation of $beta_1$ and $beta_2$ adrenoceptors in rat myocardium following isoprenaline infusion. *Br. J. Pharmac.*, **95**, 820P.

Massie, B., Bourassa, M., Dibianco, R., Hess, M., Konstam, M., Likoff, M. & Packer, M. (1985). Long term oral administration of amrinone for congestive heart failure. Lack of efficacy in a multicentre controlled trial. *Circulation*, **71**, 963–971.

Mattson, H., Hedberg, A. & Carlsson, E. (1982). Intrinsic sympathomimetic activity of the partial agonist prenalterol in relation to beta adrenoceptor interaction in various tissues *in vitro*. *J. Pharmac. exp. Ther.*, **224**, 654–661.

Morad, M. (1982). Ionic mechanisms mediating the inotropic and relaxant effects of adrenaline on the heart muscle. In *Catecholamines in the non-ischaemic and ischaemic myocardium*, eds. Oliver, M. F. & Riemersma, R. A., pp. 113–125. New York: Elsevier.

Nuttall, A. & Snow, H. M. (1982). The cardiovascular effects of ICI 118,587: A $beta_1$ adrenoceptor partial agonist. *Br. J. Pharmac.*, **77**, 381–388.

Persson, C. G. A., Erjefact, I. & Andersson, K. E. (1983). Positive inotropic and chronotropic effects. A coronary vasodilation *in vitro* by two anti asthmatic xanthines with different abilities to antagonise adenosine. *J. cardiovasc. Pharmac.*, **5**, 778–785.

Pouleur, H., Rousseau, M. F., Mengeot, P., Veriter, C., Vincent, M. F. & Brasseur, L. A. (1982). Improvement of global and regional left ventricular function in patients with previous myocardial infarction by a new $beta_1$ adrenoceptor partial agonist ICI 118,587. *Eur. Heart J.*, **3** (suppl. D), 123–127.

Pouleur, H., Vaneyll, C., Cheron, P. *et al.* (1986). Changes in left ventricular filling dynamics after long term xamoterol therapy in ischaemic left ventricular dysfunction. *Heart Failure*, **2**, 176–184.

Raijfer, S. I., Anton, A. H., Rosen, J. D. & Goldber, L. I. (1984). Beneficial haemodynamic effects of oral laerodopa in heart failure: relation to generation of dopamine. *New Engl. J. Med.*, **310**, 1357–1362.

Reuter, H. (1979). Properties of two inward currents in the heart. *Ann. Rev. Physiol.*, **41**, 413–424.

Rousseau, M. F. & Pouleur, H. (1983). Sustained beneficial effects of corwin and new $beta_1$ partial agonist in moderate heart failure. *Eur. Heart J.*, **4** (suppl. E), 26.

Rousseau, M. F., Pouleur, H. & Vincent, M. F. (1983). Effects of a cardioselective $beta_1$ partial agonist (Corwin) on left ventricular function and myocardial metabolism in patients with previous myocardial infarction. *Am. J. Cardiol.*, **51**, 1267–1274.

Ruffolo, R. R. (1982). Important concepts of receptor theory. *J. auton. Pharmac.*, **2**, 277–295.

Ruffolo, R. R. (1987). Review: The Pharmacology of Dobutamine. *Am. J. med. Sci.*, **294**, 244–248.

Sato, H., Inoue, M., Matsuyama, T., Ozaki, H., Shimazu, T., Takeda, H., Ishida, Y. & Kamada, T. (1987). Haemodynamic effects of the $beta_1$ adrenoceptor partial agonist xamoterol in relation to plasma norepinephrine levels during exercise in patients with left ventricular dysfunction. *Circulation*, **75**, 213–220.

Scholz, H. (1980). Effects of beta and alpha adrenoceptor activators and adrenergic transmitter releasing agents on the mechanical activity of the heart. In *Handbook of Experimental Pharmacology*, ed. Szekeres, L., pp. 651–733. Berlin, New York: Springer.

Sharma, B. & Goodwin, J. F. (1978). Beneficial effects of salbutamol on cardiac function in severe congestive cardiomyopathy: Effect on systolic and diastolic function of the left ventricle. *Circulation*, **58**, 449–453.

Swedberg, K., Hjalmarson, A., Waagstein, F. & Wallentin, I. (1980a). Beneficial effects of long term beta blockade in congestive cardiomyopathy. *Br. Heart J.*, **44**, 117–133.

Swedberg, K., Hjalmarson, A., Waagstein, F. & Wallentin, I. (1980b). Adverse effects of beta blockade withdrawal in patients with congestive cardiomyopathy. *Br. Heart J.*, **44**, 134–142.

Tada, M. & Katz, A. M. (1982). Phosphorylation of the sarcoplasmic reticulum and sarcolemma. *Ann. Rev. Physiol.*, **44**, 401–423.

Thomas, J. A. & Marks, B. H. (1978). Plasma norepinephrine in congestive heart failure. *Am. J. Cardiol.*, **41**, 233–243.

Tsien, R. W. (1983). Calcium channels in excitable cell membranes. *Ann. Rev. Physiol.*, **45**, 341–358.

Unverferth, D. V., Magorien, R. D., Lewis, R. P. & Leier, C. V. (1980a). Long term benefit of dobutamine in patients with congestive cardiomyopathy. *Am. Heart J.*, **69**, 262–266.

Unverferth, D. V., Blanford, M., Kates, R. E. & Leier, C. V. (1980b). Tolerance to dobutamine after a 72 hour continuous infusion. *Am. J. Med.*, **69**, 262–266.

Waagstein, F., Reiz, S., Ariniego, R. & Hjalmarson, A. (1981). Clinical results with prenalterol in patients with heart failure. *Am. Heart J.*, **102**, 548–554.

Wetzel, B. & Hauer, N. (1988). New cardiotonic agents: A promising approach for treatment of cardiac failure. *Trends pharmac. Sci.*, **9**, 166–170.

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