Inotropic agents for heart failure: what if digoxin increases mortality?

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In recent years the approach to heart failure has changed from one that focused on the haemodynamic changes at the basis of the syndrome or occurring as a result of it to one that recognises the significance of neuroendocrine activation not only for the occurrence of heart failure but also for its clinical expression and ultimate prognosis. Moreover, the fact that heart failure depends not only on cardiac changes but to a large extent on intrinsic peripheral changes has been gradually appreciated.

Consequently, the management of heart failure has taken a different turn, focusing now on modulation of neuroendocrine activation and other extracardiac abnormalities rather than trying to increase cardiac contractile force through positive inotropic treatment. This attitude has been reinforced by current doubts about the clinical efficacy and safety of positive inotropic treatment. As other physiologically more relevant treatments such as inhibition of angiotension converting enzyme have become available, it is not so much a question of when positive inotropic agents should be administered but whether there is in fact a place and need for this form of treatment.

In most patients, however, cardiac contractile dysfunction is the primary disorder and the origin of the heart failure, so intuitively, pharmacological interventions aimed at inotropic support have been considered important in treating heart failure for many years. Consequently, many inotropic agents have been developed. Positive inotropic drugs are categorised as cyclic AMP (cAMP) dependent or cAMP independent.

Cardiac contractile force and contractility: how to manipulate it?

cAMP DEPENDENT MECHANISMS

Whether they act through cAMP or not, inotropic drugs increase cardiac contractile force by altering the availability of calcium to the contractile proteins and by altering the interaction of calcium with the troponin-tropomyosin complex. In addition, cAMP dependent agents influence the velocity of contractile protein interaction and the sequestration of calcium from the cytosol after contraction.

cAMP formation depends on the activity of the adenylate cyclase system, which, in turn, depends on activation of stimulatory β adrenergic versus inhibitory muscarinic or adenosine receptors and on the activity of stimulatory versus inhibitory regulating

proteins, the G proteins (fig 1). Once formed, cAMP is degraded to 5-AMP under the influence of soluble or membrane bound cGMP inhibited, cAMP specific phosphodiesterases of subtype III.

In the heart an increase of this second messenger leads to cAMP dependent phosphorylation of certain protein kinases, which affect the contraction-relaxation process in several ways. Firstly, the slow inward calcium current is increased through voltage dependent L type channels in the sarcolemma. This calcium is instrumental in the subsequent release of larger amounts of calcium from the sarcoplasmic reticulum into the cytosol at the contractile protein site. The degree of calcium induced calcium release determines the force of contraction.

Secondly, the concentration of cAMP is pivotal for myofibrillar ATPase activity and crossbridging cycling rate, and, hence, for contractility.

Finally, cAMP influences relaxation in various ways. Phosphorylation of phospholamban enhances calcium reuptake by the sarcoplasmic reticulum, whereas phosphorylation of troponin I reduces the calcium sensitivity of troponin C, both mechanisms enhancing cardiac relaxation.

cAMP INDEPENDENT MECHANISMS

There are several additional ways to interfere with cardiac contraction without affecting cAMP concentrations. Again, in these cAMP independent mechanisms calcium plays a central part. Experimental conditions which increase the intracellular calcium concentration directly or indirectly by introducing paired stimulation enhance contractile force in parallel with the change in inward calcium current.¹ For instance, α_1 adrenergic receptor stimulation increases inositol 1,4,5-triphosphate (IP3) concentrations, subsequently enhancing the inward calcium current and contractile force, whereas sarcolemmal calcium agonists may increase force by directly opening the calcium channels—for example, Bay K 8644.² However, potentially more relevant mechanisms in terms of pharmacological modulation of intracellular calcium relate to either sarcolemmal sodium channel stimulation or to sarcolemmal sodium-potassium ATPase inhibition (digitalis glycosides), the latter indirectly raising the concentration of intracellular calcium ions through increased sodium influx with subsequent sodium-calcium exchange.

A different approach towards increasing contractility is not to increase the

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Figure 1 Schematic representation of cardiac cyclic AMP (cAMP) formation and its interaction with contraction and relaxation. cAMP, formed after activation of the β receptor (R_s)- G_s -adenylate cyclase axis, stimulates several protein kinases, subsequently enhancing sarcolemmal calcium fluxes, which release calcium from intracellular stores, such as the sarcoplasmic reticulum. Binding of calcium with the troponin-tropomyosin complex (Ti, Tc, Tm, Tt) leads to actin-myosin interaction and contraction. Subsequent sequestration of cytosolic calcium into the sarcoplasmic reticulum and relaxation is enhanced by cAMP induced phosphorylation of protein kinases that affect the activity of phospholamban and Ti. cAMP is degraded to 5-AMP under the influence of cytosolic and particulate cyclic nucleotide phosphodiesterases. (M, muscarinic; P, purinergic; R_i , inhibitory receptor; G_i , inhibitory G protein.)

concentration of calcium but to enhance the sensitivity of the contractile apparatus—that is, of troponin C—for the available calcium. Cardiac contraction is governed by three mechanisms: increase in intracellular calcium concentration, the binding of calcium to troponin C, and subsequent alteration of molecular conformation of the myofibrils. Calcium occupancy of troponin C is determined by the ratio of the rates of association and dissociation of calcium. As it is the latter which is affected by manoeuvres that improve calcium sensitivity, it follows that, as a consequence, relaxation may slow down.³

Calcium sensitisation is potentially an interesting approach to positive inotropic support in heart failure. Apparently, it is more economical and less energy consuming to increase contractile force than increase the intracellular concentration of calcium, particularly by cAMP dependent mechanisms—for example, with agents such as isoprenaline and the predominant phosphodiesterase inhibitors, such as enoximone.⁴ The reasons are twofold. Firstly, the energy required for calcium recycling increases with higher inward calcium currents. Secondly, myofibrillar ATPase activity is amplified with cAMP dependent inotropic mechanisms. By contrast, increasing cardiac force by enhanced calcium sensitivity or enhanced maximum calcium activated force avoids this extra myocardial energy consumption.

Moreover, calcium sensitisation may be preserved in progressive heart failure,⁵ despite the fact that ionic conditions such as acidosis and increased phosphate concentrations,⁶

prevalent in ischaemia and possibly also in ischaemic cardiomyopathy and end stage heart failure, negatively affect calcium sensitivity. In contrast, cAMP dependent contractile effects become progressively less during the later stages of heart failure.^{7,8}

Intrinsic cardiac changes during heart failure that affect pharmacological inotropic interventions

Secondary to the enhanced sympathetic stimulation in heart failure, sarcolemmal β receptor density decreases significantly as a result of internalisation of the receptor and of uncoupling.⁹ Consequently, adrenergic stimulation results in progressively less adenylate cyclase activity and cAMP formation. Moreover, there is enhanced expression of the inhibitor subunit of the guanine-nucleotide-binding regulatory proteins, $G_{i\alpha}$,^{10,11} which reduces cAMP formation. This increase in the level of $G_{i\alpha}$ is unrelated to muscarinic M_2 or A_1 adenosine receptor activity.¹² Furthermore, stimulation of adenylate cyclase by colforsin may be reduced in heart failure.¹³ Consequently, not only is basal cAMP formation decreased in heart failure but also the potential to stimulate it pharmacologically is diminished.

Initially, a specific decrease in the β_1 subtype was assumed, leading to a 50–70% downregulation of β receptors.¹⁴ By contrast, β_2 receptors were not believed to be down-regulated, suggesting a potential therapeutic role. Recent studies by Bristow *et al* indicate, however, that moderate (25–35%) uncoupling of β_2 receptors occurs in heart failure,¹⁵ albeit predominantly in patients with ischaemic cardiomyopathy. These authors suggested that the regulatory behaviour of components of the β receptor G protein-adenylate cyclase axis differed between idiopathic dilated and ischaemic cardiomyopathy, with β_1 receptor downregulation in the first and uncoupling of β_2 receptors in the latter patient group.⁹ Moreover, the increase in $G_{i\alpha}$ may occur only in idiopathic cardiomyopathy.¹⁶

Consequently, changes linked to the β adrenergic receptor in heart failure have important effects on cAMP formation in the heart. Deficient cAMP production undoubtedly is an important cause of contractile dysfunction in heart failure and of the lack of therapeutic efficacy of cAMP dependent positive inotropic support.

Moreover, the high adrenergic drive during heart failure which leads to these receptor changes also causes marked depletion of neurotransmitters in the heart. Both in idiopathic dilated cardiomyopathy and in ischaemic cardiomyopathy, tissue noradrenaline, adrenaline, dopamine, and neuropeptide Y concentrations are decreased.⁹ Consequently, indirect acting β agonists, such as doxamine and dopamine, lose their efficacy over time.

By contrast, cAMP independent inotropic mechanisms are possibly less affected by intrinsic cardiac changes. For instance,

myocardial α adrenergic receptor density is unchanged in heart failure.^{17 18} Although this could be important because α adrenergic stimulation elicits a positive inotropic response in humans, a diminished inotropic response has, nevertheless, been observed in heart failure, either as a result of receptor uncoupling or secondary to a general defect in the contractile potential in this condition.¹⁹ By contrast, calcium sensitisation remains intact even in advanced stages of failure, and there is no evidence for a diminished efficacy of digitalis in advanced heart failure, at least not in *in vitro* experiments. Similarly, there are no data to indicate that sodium channel stimulation or other cAMP independent ways to increase intracellular calcium concentrations lose their inotropic efficacy in end stage heart failure.

Clinical efficacy of cAMP dependent inotropic agents

SYMPATHOMIMETIC AGENTS (TABLE)
Sympathomimetic agents are undoubtedly one of the cornerstones of the treatment of acute heart failure, particularly in low output conditions and in cardiogenic shock. Parenterally administered β_1 and β_2 adrenergic agents, dopamine, and, possibly, colforsin have clearly shown acute haemodynamic and clinical efficacy.

The effect is, however, comparatively short lived. Tolerance may occur after days, probably due to reduced β receptor responsiveness secondary to further receptor downregulation, an increase in G_{ia} , and possibly also inactivation of the adenylate cyclase system. Consequently, the capacity of the heart to produce cAMP diminishes. Although early studies suggested a sustained clinical improvement lasting for several weeks after a three day infusion of dobutamine, such improvement was observed only in a minority of patients and then specifically in those with a fairly well preserved function at baseline. Subsequent attempts to obviate long term

tolerance by intermittent dobutamine administration provided some clinical efficacy, as measured by exercise capacity and clinical improvement, although baseline ventricular function remained unchanged.²⁰ Again, the improvement was observed in patients with less severe heart failure (New York Heart Association class III). In contrast, in patients with more severe failure, for whom such treatment would be more relevant, clinical improvement has not been impressive and mortality may be increased despite initial haemodynamic improvement.

Orally active sympathomimetic agents have not proved to be successful either. The β_1 agonist prenalterol, although resulting in initial haemodynamic and clinical improvement, did not lead to sustained benefit, and its use has long been discarded. Also, long term results with predominantly β_2 agonists, such as pirbuterol, terbutaline, and salbutamol, which in addition have some β_1 agonist properties, have not been favourable. Whereas early haemodynamic improvement was commonly present, this did not persist and long term clinical efficacy was inconsistent.^{21 22} Higher doses to improve efficacy have caused side effects, such as tremulousness or serious ventricular arrhythmias.²³ As a result, orally active β_2 agonists are currently not used to treat heart failure.

In contrast, the partial β_1 agonist and antagonist xamoterol has, for some time at least, been considered a useful addition to the therapeutic armamentarium in mild heart failure. Xamoterol probably does have a valuable role as an alternative to diuretics or in patients with heart failure and atrial fibrillation. It may have a special role in elderly patients with heart failure. Xamoterol may also be an excellent choice in patients with heart failure and angina. Indeed, amelioration of ischaemic left ventricular dysfunction rather than heart failure itself may be its principal mode of action. A controlled study in severe heart failure failed to show clinical improvement but showed that xamoterol increased mortality.²⁴ Preliminary reports in patients with milder heart failure suggest a neutral or slightly favourable effect on survival.

DOPAMINERGIC AGENTS

In acute heart failure dopamine is extensively used in low output conditions to improve renal flow at lower doses and to improve cardiac output and blood pressure at higher doses. This reflects the pharmacological profile of the drug, which includes stimulation of dopaminergic 1 and 2 receptors and, at higher dosages, activation of β_1 , α_1 , and α_2 receptors. However, the major inotropic mechanism of action seems to be through cardiac adrenergic neurotransmitter release.²⁵ As noradrenaline stores become depleted in the course of failure the positive inotropic effect of dopamine diminishes.

The orally active dopaminergic agents, levodopa and ibopamine, have a similar profile and have positive inotropic effects as well as

Clinically evaluated positive inotropic agents

Sympathomimetic agents	Phosphodiesterase inhibitors	Agents affecting membrane pumps or channels
Non-selective: Noradrenaline (α and β) Adrenaline (α and β) Isoprenaline (β)	Predominant phosphodiesterase inhibitors: Amrinone Milrinone Enoximone Piroximone Adibendan Imazodan	Sodium channel stimulants: DPI 201-106 (partial calcium sensitiser) PD 122 860
Predominant β_1 agonists: Dobutamine Prenalterol (partial agonist) Xamoterol (partial agonist)	Partial phosphodiesterase inhibitors/calcium sensitisers: Sulmazole Pimobendan Isomazole UK-61 260 Org 30029 MCI-154	Vesnarinone (partial phosphodiesterase inhibitor; affects outward and inward rectifying potassium current)
Predominant β_2 agonists: Dopexamine (partial dopaminergic) Salbutamol Pirbuterol Terbutaline		Sodium-potassium ATPase inhibitors: Digitalis glycosides
Dopamine and β_1 agonists: Dopamine Levodopa Ibopamine*		
Adenylate cyclase stimulant: Colforsin		

*Possibly only dopaminergic at clinically relevant dosages (see text).

Figure 2 Regional vasodilator effect of locally administered milrinone. Forearm blood flow increases and forearm vascular resistance decreases parallel to incremental dosages of milrinone, which result in detectable milrinone concentrations in forearm venous blood (■) but undetectable circulating concentrations (□).²⁸ Reproduced with permission.

vasodilator actions on renal, cerebral, coronary, and visceral beds (postsynaptic dopaminergic-1 action), and modulating effects on noradrenaline release from nerve endings (presynaptic dopaminergic-2 action). Evidence in humans that these agents affect contractility under standard pharmacological concentrations is scarce. Recent data suggest that ibopamine, the only orally active dopaminergic agent available for clinical use, may be a (renal) vasodilator rather than a positive inotropic agent.²⁶

cAMP PHOSPHODIESTERASE INHIBITORS

By contrast to the lack of inotropic effects of orally active dopaminergic agents, cAMP phosphodiesterase (PDE) inhibitors clearly improve cardiac contractility in humans, shown when agents such as milrinone are introduced into the coronary circulation.²⁷ PDE inhibitors are also potent vasodilators, as may be observed after intra-arterial administration in heart failure (fig 2).²⁸ Consequently, PDE inhibitors are better classified as inodilators than positive inotropic agents.²⁹ Venodilating properties may predominate with these compounds, at least at lower doses,^{30 31} and, in patients with normal to low ventricular filling pressures as a result of diuretic treatment, PDE inhibition may reduce cardiac output by reducing filling pressures still further, an effect which resembles that of nitrates under similar conditions (fig 3).³²

In addition, tolerance to their vasodilating properties may occur. After long term treatment with milrinone in patients with moderate heart failure, the initial improvement in pump function disappears, whereas after withdrawal, cardiac output decreases and systemic resistance increases beyond pretreatment values.³³ This rebound phenomenon may reflect neurohormonal activation during milrinone treatment.

Whether or not related to haemodynamic tolerance, there is ample evidence that clinical efficacy with predominant PDE inhibitors is not sustained. In placebo controlled studies

with agents such as amrinone and enoximone significant improvements in exercise capacity or clinical wellbeing have not been sustained.^{34 35} One study that compared milrinone, digoxin, their combination, and placebo in patients with class III heart failure (New York Heart Association's classification) suggested an improvement with the PDE inhibitor.³⁶ However, in this study, all patients were initially taking digoxin, which was withdrawn before randomisation. Although patients taking milrinone had better exercise capacity than the patients who received placebo, when they were compared with patients who continued to take digoxin there was no such effect. Rather than supporting the efficacy of milrinone, this study would favour the use of digoxin in moderate to severe heart failure.

Clinical efficacy of cAMP independent inotropes

CALCIUM SENSITISERS

By contrast to predominant PDE inhibitors, late haemodynamic tolerance may not be a problem with the few available calcium sensitisers, which all share some PDE inhibiting effects (table). Pimobendan, a calcium sensitiser and partial PDE inhibitor and the most extensively studied compound in this category, retains its vasodilating capacity and haemodynamic efficacy for at least six months in patients with moderate heart failure.³⁷ This indicates that long term haemodynamic effects may differ between predominant PDE inhibitors and compounds which share calcium sensitising and PDE inhibiting properties. Also, long term clinical efficacy may differ. Available controlled studies indicate an improvement in exercise capacity, peak oxygen consumption, and heart failure status after treatment lasting between three and six months.³⁸⁻⁴⁰ Whereas this may already be true for fairly high doses of pimobendan, it is interesting to note that clinical efficacy is better with low to intermediate doses.³⁹ Whether this reflects relatively less PDE inhibition at lower doses is as yet purely speculative.

Theoretically, calcium sensitisation may further slow the process of myocardial relaxation, which is already impaired in heart failure. In myopathic tissue the capacity to restore normal concentrations of cytosolic calcium during diastole is diminished. Consequently, both resting intracellular calcium concentrations and diastolic developed force are higher than in normal cardiac muscle. As this negatively affects contractile force, "pure" calcium sensitisers may further decrease contractile reserve in addition to their effect on relaxation.³ This is, however, less likely for the calcium sensitisers currently available, which all have additional PDE inhibiting properties. Pimobendan, administered intravenously to patients with heart failure (New York Heart Association class II-III) and ischaemic cardiomyopathy, impairs neither ventricular relaxation nor contractility (fig 4). Instead, isovolumetric relaxation indices improve,

Figure 3 Effect of oral milrinone (10 mg) on cardiac pump function in nine patients with heart failure and raised left ventricular filling pressures (PCWP) (■; PCWP ≥ 18 mm Hg) and nine patients with heart failure and normal left ventricular filling pressures (○; PCWP < 18 mm Hg). (Heart failure was class II-III according to classification of New York Heart Association.) Cardiac index improves in the first group but falls in the second.³² Reproduced with permission.

Figure 4 Acute, but sustained improvement of isovolumetric indices of contractility (LV dP/dt positive and V_{ca40}) and relaxation (T_1 and T_2) after 10 mg intravenous pimobendan in patients with ischaemic cardiomyopathy and moderate heart failure. During the measurements heart rate was fixed by way of atrial pacing. (T , tau (relaxation time constant).)

which, together with its acute vasodilating effects under these conditions, may represent the additional PDE inhibiting properties of this compound.⁴¹ Myocardial energetics are also favourably affected with a decrease in myocardial oxygen consumption. This contrasts with predominant cAMP dependent interventions—that is, xamoterol and enoximone—which under similar conditions increase oxygen consumption or leave it unaffected.^{42 43}

SODIUM CHANNEL STIMULANTS

The few available sodium channel stimulants (table) have additional vasodilating properties, although they primarily induce positive inotropic effects through sodium channel stimulation and subsequent sodium-calcium exchange.^{44 45} Like the available calcium sensitizers, this suggests that these agents should be considered inodilators rather than pure positive inotropes.

The most intensively studied sodium channel stimulant in humans is OPC 8212 (vesnarinone); it was recently shown to enhance survival in patients with severe heart failure when given in low doses.⁴⁶ This interesting and unexpected finding for a positive inotrope may relate to the additional pharmacological properties of this rather complex molecule. Besides sodium channel stimulating effects and mild, selective PDE inhibition, vesnarinone decreases the delayed outward and inward rectifying potassium currents. The latter are probably involved in the antitachycardiac effects of vesnarinone, observed after sympathetic stimulation, and in the prolongation of the action potential.⁴⁷ Whether this implies that vesnarinone should be considered a class III antiarrhythmic agent

Figure 5 Biphasic pattern of constriction after ouabain has been added to coronary vascular strips. The first contraction is the direct effect of the drug and depends on available calcium. The second is absent in denervated strips and reduced after α blockade with prazosin, indicating noradrenaline release by digitalis.⁴⁹ Reproduced with permission.

rather than an inotrope, and, consequently, the effects on mortality the result of an antiarrhythmic effect, is uncertain. Firstly, Feldman *et al* found that the reduction in mortality applied not only to patients dying suddenly but also to patients dying of progressive failure.⁴⁶ Moreover, vesnarinone reduced the risk of worsening heart failure and improved quality of life. Secondly, available antiarrhythmic agents have thus far not appreciably affected mortality in progressive heart failure. The reasons for the unexpected beneficial effect of vesnarinone on survival and heart failure status are not clear, but they may include the combination of cAMP independent inotropic effects, antiarrhythmic properties, a bradycardiac effect, and, possibly, an inhibiting action on cytokine production.⁴⁸

There is some concern, though. Vesnarinone induces agranulocytosis in 2.5% of patients. Moreover, as will be discussed below, it probably has a narrow therapeutic range, like digitalis.⁴⁶

DIGITALIS GLYCOSIDES

Digitalis glycosides inhibit the activity of membrane sodium-potassium ATPase. This results in raised intracellular sodium, which is exchanged for calcium through the sodium-calcium exchanger. In addition, the rise in intracellular calcium concentration leads to an increase in hydrogen ions, which are exchanged for sodium, in turn leading to more intracellular calcium. This results in enhanced cardiac contractility and vasoconstriction.

In vitro, the vasoconstrictor effects of digitalis are biphasic.⁴⁹ Firstly, there is a contraction which depends on available calcium and reflects the direct constrictor effect of the drug. This is followed by a second vasoconstriction, which is lost in denervated vascular strips and reduced by co-administration of the α_1 blocker prazosin, probably by digitalis induced release of noradrenaline from nerve endings (fig 5). In vivo these direct vasoconstrictor effects of

digitalis are augmented through central stimulation of sympathetic tone.⁵⁰

In subjects with normal cardiac function digitalis has a vasoconstrictor effect, although this depends on dose and rate of administration. Intravenous administration of ouabain for 10 seconds or two minutes causes a significant increase in systemic vascular resistance but not when a slower infusion rate is applied.⁵¹ In subjects without heart failure an intravenous bolus administration of digoxin results in coronary vasoconstriction with a significant reduction in the cross sectional area of both normal segments and arteries with coronary artery disease.⁵²

In heart failure the acute vasoconstrictor action of digitalis is counteracted by the modulating effects of digitalis on neuro-hormonal activation and by its sympatho-inhibitory activity. Thus, in patients with heart failure digitalis may induce vasodilatation through direct or indirect attenuation of neuroendocrine activation. In addition to earlier observations by Mason and Braunwald of the peripheral vasodilating effects of ouabain in patients with heart failure and of vasoconstriction in normal subjects,⁵⁰ Ferguson *et al* recently showed that short term treatment with digitalis reduces sympathetic nerve activity, resulting in systemic vasodilatation in patients with heart failure but not in normal subjects.⁵³ Glycosides increase baroreceptor sensitivity, both in normal subjects and in patients with heart failure. Underlying mechanisms may include direct receptor stimulation, an effect related to inhibition of sodium-potassium ATPase, or a secondary response to improved haemodynamics. The findings of Ferguson *et al* suggest a direct effect, as sympathoinhibitory effects occurred before haemodynamic changes were apparent.⁵³

Short term treatment with digitalis also leads to a reduction in circulating catecholamine concentrations, plasma renin activity, and aldosterone concentrations. In addition, in vitro data indicate that ouabain may stimulate secretion of atrial natriuretic peptide from atrial cardiocytes.⁵⁴ Recently the Dutch ibopamine multicentre trial, a six month comparison of ibopamine, digoxin, and placebo in patients with moderate heart failure taking diuretics, indicated that digoxin also significantly decreases circulating noradrenaline and renin concentrations.⁵⁵ Thus, digitalis emerges as an interesting drug for managing heart failure, as it combines both cAMP independent positive inotropic properties and neurohormonal modulating effects.

But does it work in clinical practice? There is little doubt about its efficacy in patients with heart failure and atrial fibrillation, partly because of its vagotonic effect. By contrast, despite its early recognition as a therapeutic agent for dropsy⁵⁶ and the elaborate studies by Withering,⁵⁷ its usefulness in heart failure and sinus rhythm has been and still is being debated. Whereas long term haemodynamic improvement is clear, many studies that have explored the clinical effects of digoxin have

not shown convincing benefit.⁵⁸⁻⁶⁴ Few adequate controlled studies of digoxin exist. Several included only patients in whom digitalis could be withdrawn, hence introducing bias. Enrolment criteria often were not well defined—for example, the presence of systolic dysfunction and background treatment were not controlled for or specified and sample size was often inadequate.

A few studies have indicated that the addition of digitalis to existing treatment or its withdrawal under controlled conditions leads to clinical improvement or deterioration, respectively.⁶⁵⁻⁶⁷ Patients with heart failure and sinus rhythm who improved tended to be those with systolic dysfunction, large hearts, an S3 gallop, and heart failure (New York Heart Association class III) despite treatment. By contrast, the Dutch ibopamine multicentre trial suggested that digoxin exerted clinical benefits even in patients with moderate heart failure who were treated only with diuretics.⁵⁵ Two recent studies in patients with mild to moderate heart failure and sinus rhythm indicate that such patients also tend to deteriorate after abrupt withdrawal of digitalis.^{68,69} The RADIANCE study is particularly noteworthy in this respect, as all patients in this study, in contrast to previous investigations with digitalis, were taking ACE inhibitors⁶⁹ (fig 6). Thus, when clinical efficacy is concerned, it makes sense to give digitalis to patients with comparatively severe heart failure and sinus rhythm despite the accepted standard treatment of diuretics and ACE inhibitors. Also, it makes sense to continue digitalis when such patients have improved to a milder stage of heart failure. But how safe is digoxin?

What if digoxin increases mortality?

Despite centuries of use, doctors do not know whether digitalis has an effect on mortality and whether this is favourable. Arrhythmias are a well recognised manifestation of digitalis toxicity. The therapeutic-toxic dose range is quite narrow under normal conditions; aging, abnormal renal haemodynamics, and the propensity for hypokalemia in heart failure may clearly enhance the potential for toxicity.

Figure 6 Worsening of exercise capacity in patients with mild heart failure previously taking digoxin, diuretics, and ACE inhibitors in whom digoxin was replaced by placebo. The comparison group continued to take digoxin.⁶⁹ Reproduced with permission.

As suggested above, the clinical efficacy of digitalis is probably better in more severe conditions where pharmacokinetic aspects could be more disadvantageous. Yet, several fairly large comparative studies of digitalis in patients with severe heart failure did not report a significant increase in ventricular ectopic activity.^{63 66 70} Moreover, a proarrhythmic effect does not necessarily lead to increased mortality in heart failure.

Digitalis could also beneficially affect survival by improving cardiac function, by its sympathoinhibitory and neurohormonal modulating effects, and by its parasympathomimetic properties. Its inotropic effect may primarily occur at higher doses and its neurohormonal effect at lower doses.⁷¹ Although this assumes less detrimental effects with low dose digitalis—in line with the experiences with vesnarinone and possibly enoximone—this is still speculative.

As with other positive inotropes, a large trial of digoxin is needed to assess its effects on survival at different stages of heart failure, preferably with monitoring of serum digoxin concentrations and against the background of currently accepted treatment for heart failure. Such a study is presently being conducted in over 8000 patients—the DIG trial. If this trial shows a favourable effect of digoxin on survival then it is likely that all patients with established heart failure will be treated with digoxin and an ACE inhibitor, diuretics retaining their role when fluid retention is a problem. If digoxin's effect on mortality is neutral then the knowledge that digoxin is safe will also lead to more widespread use. On the other hand, if digoxin increases mortality use will decline. Most of the properties that have been imputed to digoxin at one time or another have already been proved with ACE inhibitors: symptomatic improvement, delays in the deterioration of heart failure, and increased survival. However, digoxin seems to have a role in improving symptoms in addition to that of an ACE inhibitor. Many physicians may wish to continue to use digoxin in severe heart failure, believing that the relief of symptoms is a sufficient reward for the increase in mortality. This is similar to what recently happened with flosequinan, a new agent for heart failure. The medicolegal position in that case was considered to be untenable, and the drug was withdrawn. Will a similar situation develop with digoxin, the medicolegal threat not being to a pharmaceutical company but to prescribing doctors?

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