Inotropic Drugs and Their Mechanisms of Action

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This report describes various old and new positive inotropic drugs with respect to their mechanisms of action. Drugs with established cardiotonic effects include cardiac glycosides, beta-adrenergic agents, glucagon, histamine and the methylxanthines. New agents discussed are prenalterol, beta-, and alpha-adrenergic drugs, amrinone and sulmazole. Prenalterol is a beta-adrenergic agent. Betax-adrenergic drugs, amrinone and sulmazole, combine a positive inotropic and a vasodilator effect.

Agents that increase the force of contraction of the heart are referred to as positive inotropic or cardiotonic drugs. The increase in the force of myocardial contraction is ultimately due to an increase in intracellular free Ca\(^2+\) [Ca\(^2+\)], to interact with the contractile proteins or to an increased sensitivity of the myofilaments for Ca\(^2+\), or both. This report discusses how these variables might be affected by various inotropic drugs. Agents with established inotropic effect, such as cardiac glycosides, beta-adrenergic drugs, methylxanthines, glucagon and histamine, are described first. The second part of the report is concerned with new cardiotonic agents or those still under investigation. These include prenalterol, beta-adrenergic and alpha-adrenergic drugs, amrinone and sulmazole. For a more comprehensive discussion of the topic and a more extensive bibliography, the reader is referred to several recent reviews (1–6).

Mechanisms Activating Contraction and Relaxation of Cardiac Muscle

All cardiotonic drugs interact with one or more of the steps involved in contraction and relaxation of the heart (Fig. 1) (7–11). Depolarization of the sarcolemma, that is, the Na\(^+\)-dependent upstroke of the action potential, is the initial event. The depolarization of the cell membrane allows Ca\(^2+\) to move down its electrochemical gradient and enter the cell from the extracellular space during the plateau phase of the action potential (slow Ca\(^2+\) inward current [I\(_{ca}\)]; Fig. 1, step 1). The major part of the Ca\(^2+\) entering the cell during the action potential serves to fill intracellular stores (presumably the subsarcolemmal cisternae of the sarcoplasmic reticulum) and trigger the release of Ca\(^2+\) from the sarcoplasmic reticulum into the cytosol to react with the contractile proteins (Fig. 1, step 2). The mean rest level of [Ca\(^2+\)], is about 0.3 µM; the activation of the contractile proteins requires an increase to above this value with half maximal and maximal responses occurring at about 2 µM and 10 µM, respectively (12). Relaxation occurs on lowering the [Ca\(^2+\)] to below the rest level. This results from the uptake of Ca\(^2+\) by the longitudinal part of the sarcoplasmic reticulum (Fig. 1, step 3). Finally, there is an extrusion of Ca\(^2+\) to the extracellular space to avoid a Ca\(^2+\) overload. This transport of Ca\(^2+\) out of the cell is achieved mainly through a Ca\(^2+\)/Na\(^+\) exchange system (Fig. 1, step 3).

This article is part of a continuing series of informal teaching reviews devoted to subjects in basic cardiology that are of particular interest because of their high potential for clinical application.
4) that, under equilibrium conditions, follows the equation:

$$[\text{Ca}^{2+}]_i = \frac{[\text{Na}^+]_o^n \exp(n - 2) F V}{RT}$$

where \(n\) is the number of Na\(^+\) that exchanges for one Ca\(^{2+}\) ion, \(V\) is the membrane potential and \(F\), \(R\) and \(T\) are the Faraday constant, the universal gas constant and the absolute temperature, respectively (13). Its driving force is the concentration gradient for Na\(^+\) across the sarcolemma which, in turn, is accomplished largely by the sarcolemmal sodium pump, (Na\(^+\) + K\(^+\))-ATPase (Fig. 1, step 6). The exact stoichiometry of the Ca\(^{2+}\)/Na\(^+\) exchange system has not yet been resolved, but it is important to note in the present context (especially with respect to the cardiac glycosides) that only a very small increase in \([\text{Na}^+]_i\) is required to achieve a relatively large increase in \([\text{Ca}^{2+}]_i\), and, hence, in the force of contraction.

A smaller amount of Ca\(^{2+}\) efflux may also be mediated by a sarcolemmal Ca\(^{2+}\) pump that uses adenosine triphosphate in a fashion analogous to the sodium pump.

Established Cardiotonic Drugs

Cardiac Glycosides

The cardiac glycosides remain the most commonly used agents for the long-term management of congestive heart failure. It is generally accepted that these drugs ultimately lead to an increase in the amount of intracellular Ca\(^{2+}\) available to react with the contractile proteins, but the exact mechanisms through which this can be achieved are still a matter of considerable debate (14–17). There is no doubt that the cardiac glycosides interact with the (Na\(^+\) + K\(^+\))-ATPase and that this enzyme represents the “cardiac glycoside receptor,” but the subsequent steps are unsettled.

Inhibition of (Na\(^+\) + K\(^+\))-ATPase activity. Many authors argue that inhibition of (Na\(^+\) + K\(^+\))-ATPase activity is the most important event. The inhibition of Na\(^+\) transport out of the cell results in an increase in the intracellular Na\(^+\) concentration which, by way of an effect on the transsarcolemmal Ca\(^{2+}\)/Na\(^+\) exchange described earlier, leads to an increase in \([\text{Ca}^{2+}]_i\). In other words, the accumulation of Na\(^+\) at the inside of the sarcolemma competitively inhibits the efflux of Ca\(^{2+}\) by way of the Ca\(^{2+}\)/Na\(^+\) exchange system that normally carries Ca\(^{2+}\) out of the cell. The result of the decrease in Ca\(^{2+}\) efflux is an increase in \([\text{Ca}^{2+}]_i\). This view has recently gained considerable support by Lee and Da-gostino (18) and Wasserstrom et al. (19), who showed through the use of Na\(^+\)-sensitive intracellular microelectrodes that changes in intracellular Na\(^+\) activity and in twitch tension produced by therapeutic concentrations of cardiac glycosides were closely correlated. Quantitatively, a 1 mM increase in intracellular sodium activity (which is barely detectable with chemical methods) was accompanied by about a 100% increase in force of contraction.

Other investigators (15) assume that such an inhibition of (Na\(^+\) + K\(^+\))-ATPase activity is only important during toxic actions of these agents. The interaction of therapeutic concentrations with the (Na\(^+\) + K\(^+\))-ATPase would not necessarily inhibit the enzyme, but instead could lead to a less stable Ca\(^{2+}\) binding within the sarcolemma and, hence, to an increased Ca\(^{2+}\) release from sarcolemmal Ca\(^{2+}\) stores during excitation (Fig. 1, step 5). This view, however, is still highly controversial.

Increase in \(I_{\text{d}}\). Another still unresolved question is the effect of cardiac glycosides on the slow Ca\(^{2+}\) inward current \(I_{\text{d}}\). Some authors found that cardiac glycosides increase \(I_{\text{d}}\), but this was not in accord with reports from others (20, 21). However, the reported increase in \(I_{\text{d}}\) apparently did not result from a direct interaction between drugs and slow channels, but instead was indirect and resulted from an increase in \([\text{Ca}^{2+}]_i\), achieved by other mechanisms. Moreover, the changes in Ca\(^{2+}\) influx by way of \(I_{\text{d}}\) did not appear to be absolutely required for positive inotropy. Thus, I be-
lieve it that the most plausible mechanism of the cardiotonic effect of the cardiac glycosides at present is an increase in [Ca\(^{2+}\)] due to (Na\(^{+}\) + K\(^{+}\))-ATPase inhibition and subsequent alteration of Ca\(^{2+}\)/Na\(^{+}\) exchange.

**Beta\(_1\)-Adrenergic Drugs**

The positive inotropic effect of the catecholamines nor-epinephrine, epinephrine, isoproterenol, dopamine and dobutamine is due mainly to stimulation of myocardial beta\(_1\)-adrenoceptors (22-29). The increase in force of contraction brought about by these agents characteristically develops very rapidly. Moreover, it is accompanied by an increase in the rate of force development (positive clinotropic effect) that is typical of almost all positive inotropic interventions (with the exception of hypothermia, for example) and is, therefore, not very distinctive. More important is a decrease in the duration of the contraction. The latter action is mainly due to a more rapid relaxation of the contraction and is, therefore, referred to as the "relaxant effect" of beta-adrenoceptor stimulation. It is noteworthy that the ability of the beta-adrenergic drugs to shorten the contraction are shared only by agents known to increase myocardial cyclic AMP (\(\alpha\)AMP) content. From a functional point of view, the relaxant effect of beta-adrenergic stimulation is important in permitting adequate ventricular filling in the face of increased heart rates.

**Effects on Ca\(^{2+}\) and cyclic AMP.** The mechanism of the positive inotropic action of beta-adrenergic catecholamines has not been elucidated in detail. However, it is generally accepted that these agents also produce an increase in Ca\(^{2+}\) concentration in the vicinity of the contractile proteins, that they lead to an increase in myocardial cAMP levels, and that the effects on both the Ca\(^{2+}\) and the cAMP systems are likely to be causally related to each other.

The main effect of the beta-adrenergic agonists on myocardial Ca\(^{2+}\) movements is to increase the slow Ca\(^{2+}\) inward current during the action potential (Fig. 1, step 1). This effect which has been attributed to an increase in the number of functional Ca\(^{2+}\) channels (30), and more recently, using the patch clamp method to record current flow through single channels, to an increase in the probability of Ca\(^{2+}\) channels to open during depolarization (31). The increase in \(I_d\) leads to an increased Ca\(^{2+}\) release from the sarcoplasmic reticulum (Fig. 1, step 2), either because it serves as a greater trigger for Ca\(^{2+}\)-dependent Ca\(^{2+}\) release or because it increases the filling of these stores with Ca\(^{2+}\) that can be released during subsequent beats. In addition, beta-adrenergic agonists lead to an increase in Ca\(^{2+}\) uptake into the sarcoplasmic reticulum (Fig. 1, step 3), which also increases the amount of releasable Ca\(^{2+}\) within and an increased Ca\(^{2+}\) release from these stores. This increase in Ca\(^{2+}\) uptake by the sarcoplasmic reticulum not only contributes to the positive inotropic properties, but also explains the relaxant effects of the beta-adrenergic agonists. However, there is some evidence that the latter might, in part, also be due to a decrease in the Ca\(^{2+}\) sensitivity of the contractile proteins (27).

It is widely accepted that the effects of beta-adrenergic agonists on myocardial Ca\(^{2+}\) movements are not direct in nature, but instead are the result of a stimulation of the adenylate cyclase with a subsequent increase in cAMP levels. cAMP leads to an activation of protein kinases and, as a result, to phosphorylation of several proteins. This changes the functional properties of the proteins, for example, their ability to bind Ca\(^{2+}\) ions, and may thus explain the beta-adrenergic effects on the calcium movements in the sarcoplasmic reticulum and possibly also in the sarcolemma.

In summary, the positive inotropic effect of beta-adrenergic drugs is mainly the result of an increase in slow Ca\(^{2+}\) inward current and in Ca\(^{2+}\) uptake into the sarcoplasmic reticulum. This, in turn, is presumably due to a cAMP-dependent phosphorylation of a variety of functional proteins. Hence, the beta-adrenergic effects on myocardial Ca\(^{2+}\) movements on the one hand and on the cAMP system on the other are probably causally related in a common pathway where the beta-adrenergic drug represents the first messenger and cAMP and Ca\(^{2+}\) represent the second and third messengers, respectively.

**Glucagon and Histamine**

Glucagon (32) and histamine (33) also have a well-established positive inotropic effect in the heart. This effect is qualitatively similar to that produced by the beta\(_1\)-adrenergic catecholamines and is also related to an increased cAMP level due to stimulation of the adenylate cyclase. However, the effects of glucagon or histamine are not mediated by beta-adrenoceptors and are not impaired by beta-adrenoceptor blocking agents, so that these drugs can be administered, at least theoretically, after pretreatment with beta-adrenoceptor blocking drugs. However, the clinical effectiveness of glucagon is not very pronounced and the therapeutic usefulness of histamine is limited by serious side-effects.

**Methylxanthines**

The methylxanthines (especially theophylline) produce not only positive inotropic, but also vasodilator effects (6,22,26,34). The former effect of theophylline is similar to that of the beta\(_1\)-adrenergic agents. It develops very rapidly (within a few seconds), is independent of the extracellular Na\(^+\) and K\(^+\) concentration, is impaired by calcium channel blocking agents such as verapamil and is also closely related to an increase in Ca\(^{2+}\) influx from the extracellular space (Fig. 1, step 1).

**Inhibition of Ca\(^{2+}\) uptake.** The positive inotropic effect of the methylxanthines has been attributed to: 1) a direct interaction with intracellular Ca\(^{2+}\) stores (inhibition of Ca\(^{2+}\) uptake by the sarcoplasmic reticulum), 2) an increase in
cellular cAMP content resulting from an inhibition of phosphodiesterase activity, 3) a blockade of receptors for endogenous adenosine (35), and 4) a sensitization of the contractile proteins to Ca$^{2+}$. The first possibility is probably significant only at high concentrations because the effect of the methylxanthines on the sarcoplasmic reticulum only occurs at concentrations greater than 1 mM which are not reached during therapy as maximal therapeutic theophylline plasma concentrations are 50 to 100 μM (35).

**Increase in cellular cAMP.** At therapeutic concentrations, the second mechanism appears to be more likely. The similarity between the positive inotropic effects of the beta-adrenergic catecholamines and theophylline suggests that an increase in myocardial cAMP levels might be involved not only in the former but also in the latter. In fact, theophylline has been shown to produce a similarly pronounced enhancement in cAMP content and in force of contraction, and the increase in cAMP in the presence of theophylline is closely correlated to an inhibition in phosphodiesterase activity (34). It is, therefore, reasonable to conclude that the increase in cAMP in the case of the methylxanthines is due to an inhibition of the degradation of cAMP, while the beta-adrenergic positive inotropic response is due to an increase in cAMP formation. In both cases, the increase in cAMP leads to the increase in slow Ca$^{2+}$ inward current which, in turn, finally produces the cardiotonic effect.

This explanation is not necessarily contradicted by the fact that the classic methylxanthines, caffeine and theophylline, especially at high concentrations, have some effects that are opposite to those of the beta-adrenergic agonists (36–38). Most importantly, millimolar concentrations usually prolong rather than reduce the duration of the contraction. However, as mentioned, at concentrations of 1 mM and more, theophylline and other methylxanthines directly inhibit the uptake of Ca$^{2+}$ by the sarcoplasmic reticulum (Fig. 1, step 3). This effect, which is independent of the cAMP system, counteracts the cAMP-dependent increase in Ca$^{2+}$ uptake and leads to a deceleration of relaxation and, hence, to a prolongation of contraction.

Thus, the prolongation of contraction in the presence of theophylline does not exclude the possibility that cAMP serves as a mediator of the positive inotropic effect of the methylxanthines. Instead, it suggests that the classic methylxanthines have cAMP-independent "side effects." In accord with this explanation, the more potent phosphodiesterase inhibitor, 1-methyl-3-isobutylxanthine, which has no direct action on the sarcoplasmic reticulum, increases the force of contraction and decreases the duration of contraction in exactly the same way as beta-adrenergic agents (isoproterenol, for example) (Fig. 2).

**Adenosine-antagonistic action.** It appears unlikely that the third mechanism mentioned, an adenosine-antagonistic action, plays a major role in the effect of theophylline on myocardial force of contraction, although this is probably of great importance in other systems (in the central nervous system, for example). In this context, the main argument is that the inotropic effects of theophylline and adenosine are opposite only in atria. While the cardiotonic effect of theophylline is similar in atrial and ventricular preparations, adenosine is negatively inotropic in the atrium, but not in ventricular cardiac muscle. In the latter, adenosine does not change contractile force at concentrations up to 10 μM, and higher concentrations of adenosine even produce a slightly positive inotropic effect (34).

**Sensitization of the contractile apparatus to Ca$^{2+}$.** This may also contribute to the cardiotonic effect of the methylxanthines. Fabiato (39) reported that the Ca$^{2+}$ sensitivity of skinned single cardiac cells was increased by caffeine (20 mM) and theophylline (10 mM). The potential importance of this effect has also been considered by Morgan and Blinks (40), who observed that millimolar concentrations of theophylline produced large inotropic effects without consistently increasing the amplitude of the signal of the Ca$^{2+}$-sensitive bioluminescent protein aequorin. However, apart from the fact that these effects were again observed only at relatively high drug concentrations, they have not been obtained by others. Herzig et al. (41), for instance, reported that theophylline or caffeine in concentrations up to 10 mM had no effect on the Ca$^{2+}$ sensitivity of the contractile proteins. This matter therefore remains controversial.

In summary, I believe that the cardiotonic action of theophylline and other methylxanthines, at least at therapeutic concentrations, is due primarily to their effect to inhibit phosphodiesterase, and, therefore, to increase cAMP levels. These effects, together with those of the beta-adrenergic catecholamines, glucagon and histamine, are schematically summarized in Figure 3. It should be noted that the increase...
in cAMP and the subsequent increase in slow Ca\textsuperscript{2+} inward current and in Ca\textsuperscript{2+} uptake into the sarcoplasmic reticulum are the most important common events in all cases. The agents differ only in the way through which this increase in myocardial cAMP content is achieved.

**New Positive Inotropic Drugs**

The ideal positive inotropic drug should, according to Opie (21), cause neither tachycardia nor arrhythmias and should not lead to a greatly increased oxygen demand. An additional vasodilation would be of advantage. Chronic use requires sufficiently high oral bioavailability and long duration of action. No pronounced tolerance should develop after prolonged treatment. The following new cardiotonic agents are discussed and evaluated in the light of these criteria.

**Prenalterol**

Prenalterol (42) is a beta-adrenergic partial agonist with relatively selective effects on beta\textsubscript{1}-adrenoceptors. In contrast to norepinephrine, epinephrine, isoproterenol, dopamine and dobutamine, the drug can be administered orally (bioavailability about 45%) and the duration of action is 4 to 6 hours. The positive inotropic effect of prenalterol has been reported to be more pronounced than its positive chronotropic action. That the ratio of inotropic to chronotropic effect may be greater for prenalterol than for other beta-adrenergic agents has been attributed to the observation that the relative amount of beta\textsubscript{1}-adrenoceptors is greater in the left ventricle than in the right atrium, at least in guinea pigs and cats (43). This argument, however, should apply to all beta\textsubscript{1}-adrenergic drugs and is, therefore, only partially conclusive. With respect to therapeutic use, it remains to be demonstrated whether prenalterol is still effective after chronic application (tolerance?) and whether and to what extent the drug may produce tachyarrhythmias.

**Beta\textsubscript{2}-Adrenergic Drugs**

Salbutamol (44), terbutaline (45), fenoterol (46) and pindolol (47) interact mainly with beta\textsubscript{2}-adrenoceptors and are preferentially used in patients with bronchial asthma. They produce positive inotropic effects (possibly due to residual beta\textsubscript{2}-adrenoceptor stimulation) and vasodilation. It is not clear which of these actions predominates in patients with myocardial insufficiency. In any case, the vasodilator effect of these drugs contributes to the increase in cardiac index and is probably of greater clinical importance than the direct cardiomodulatory action. The positive chronotropic effect of these agents is claimed to be relatively small. These drugs may be given orally (bioavailability 40 to 85%) and their duration of action is 4 to 8 hours. As in the case of prenalterol, the questions of potential tachyarrhythmias caused by cardiomodulation and of persistence of the therapeutic effect are not yet resolved.
**Alpha-Adrenergic Drugs**

There is no doubt that the positive inotropic response to adrenergic agents in the heart is mediated predominantly by beta-adrenoceptors. However, there is increasing evidence that alpha-adrenoceptors also exist in the myocardium and that an increase in force of contraction may be produced by stimulation of these sites (26, 48-50). These are alpha-adrenoceptors, and the most important drugs of this group used experimentally are phenylephrine and methoxamine. The principle of an alpha-adrenoceptor-mediated cardiotoxic action appears promising, but it should be stressed that the agents hitherto available have as yet not been used clinically for this purpose, largely because of their predominant vasoconstrictor action.

The positive inotropic effect of alpha-adrenergic agents is qualitatively different from that of beta-adrenergic drugs. The alpha-adrenergic response develops relatively slowly and is accompanied by a prolongation, rather than a shortening, of the contraction. Thus, alpha-adrenergic agents do not produce relaxant effects. Moreover, the alpha-adrenergic positive inotropic effect is not accompanied by distinct chronotropic effects, and is particularly pronounced at low stimulation frequencies, in hypothermia and in hypothyroidism.

The mechanism of the alpha-adrenergic positive inotropic response is unknown. It is generally accepted, however, that there is no increase in cAMP levels, quite in accord with the observation that there is no relaxant effect. Cyclic guanosine monophosphate (cGMP) levels and (Na\(^+\) + K\(^+\))-ATPase activity also remain unchanged. Some investigators (51) have observed a small increase in slow Ca\(^{2+}\) inward current which, however, has not been observed in all species and which is less pronounced than that produced by beta-adrenoceptor stimulating agents.

The biologic significance of alpha-adrenergic stimulation in cardiac muscle remains to be established. There is evidence that the alpha-adrenoceptors of the heart differ from those of other tissues. Thus, it appears conceivable that drugs that are positively inotropic through stimulation of myocardial alpha-adrenoceptors without vasoconstrictor effects will become available for clinical use. From the physiologic point of view, the alpha-adrenergic positive inotropic effects of catecholamines may be important under conditions where the stimulation of beta-adrenoceptors is relatively small (in hypothyroidism, hypothermia and at low heart rates).

**Amrinone**

Amrinone is a bipyridine derivative with positive inotropic, positive chronotropic and vasodilator effects (52). The positive inotropic effect develops rapidly within several minutes and the duration of action is 60 to 90 minutes. It is not impaired by beta- and alpha-adrenoceptor blocking agents, or reserpine pretreatment and histamine (H\(_1\) and H\(_2\))-receptor blocking drugs. Farah (53) Alousi (54) and their

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**Table 1. Drugs With Positive Inotropic Effects and Their Main Mechanisms of Action**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Cardiac glycosides</td>
<td>Reaction with (Na(^+) + K(^+))-ATPase, subsequent steps unsettled</td>
</tr>
<tr>
<td>Beta-adrenergic drugs</td>
<td>Increased cAMP level due to stimulation of adenylate cyclase, increase in I(s1) and Ca(^{2+}) uptake by sarcoplasmic reticulum</td>
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<tr>
<td>Norepinephrine</td>
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<td>Epinephrine</td>
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<td>Isoproterenol</td>
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<td>Dopamine</td>
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<td>Dobutamine</td>
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<tr>
<td>Glucagon and histamine</td>
<td>Increased cAMP level due to stimulation of adenylate cyclase; effect similar to that of beta(_i)-adrenergic drugs but independent of beta-adrenoceptor</td>
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<tr>
<td>Methylxanthines</td>
<td>Increased cAMP level due to inhibition of phosphodiesterase; effect similar to that of beta(_i)-adrenergic drugs (except lack of relaxant effect) but independent of beta-adrenoceptor; no evidence for adenosine antagonism</td>
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<tr>
<td>Caffeine</td>
<td>Beta-adrenoceptor stimulation, chronotropic effect relatively small; bioavailability 45%, duration of action 4 to 6 hours</td>
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<tr>
<td>Theophylline</td>
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<tr>
<td>Prenalterol</td>
<td>Positive inotropic and vasodilatation, bioavailability 40 to 85%, duration of action 4 to 8 hours</td>
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<td>Beta(_i)-adrenergic drugs</td>
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<td>Salbutamol</td>
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<td>Terbutaline</td>
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<td>Fenoterol</td>
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<td>Pirbuterol (Pfizer)</td>
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<tr>
<td>Alpha-adrenergic drugs</td>
<td>Positive inotropic effect, no chronotropic effect; no relaxant effect; no effect on cAMP</td>
</tr>
<tr>
<td>Phenytoine</td>
<td>Phosphodiesterase inhibitor; similar to theophylline; positive inotropic effect and vasodilatation</td>
</tr>
<tr>
<td>Amrinone (Winthrop)</td>
<td>Phosphodiesterase inhibitor; similar to theophylline; possible effect on Ca(^{2+}) sensitivity of contractile proteins; positive inotropic effect and vasodilatation</td>
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<tr>
<td>Sulmazole (AR-L 115 BS, Thomae)</td>
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coworkers initially reported that amrinone also does not change phosphodiesterase and (Na⁺ + K⁺)-ATPase activities or cAMP levels. This led several investigators to conclude that amrinone has an entirely new although as yet unknown mechanism of action. However, Honerjäger (55) and Endoh (56) and their coworkers showed recently that the positive inotropic effect of amrinone is accompanied by an inhibition of phosphodiesterase and an increase in cAMP. Moreover, amrinone potentiated the effects of isoprenaline and histamine and increased the rate of increase of Ca²⁺-dependent slow action potentials. From these effects, it is reasonable to assume that amrinone is not a novel drug, but is instead a phosphodiesterase inhibitor with an action similar to that of theophylline. This does not exclude the possibility that other effects could emerge (57), but the similarity between amrinone and theophylline is important because any theophylline-like drug must be regarded as a potential inducer of tachyarrhythmias. At high concentrations, amrinone produced a prolongation of the contraction. This effect is also shared by theophylline, as noted earlier.

Milrinone is a recently developed derivative of amrinone which is 10 to 30 times more potent than the parent compound. but otherwise appears to possess a similar pharmacologic profile and a similar cAMP-increasing action (58–60). However, since in the study of Alousi et al. (58) the milrinone-induced increase in force of contraction developed faster than the increase in cAMP, mechanisms other than phosphodiesterase inhibition may also be involved in the cardiotonic effect of this agent.

Sulmazole

Sulmazole (the former AR-L 115 BS) is a benzimidazole derivative with positive inotropic, positive chronotropic and vasodilator effects (61). These effects, which are similar to those of β₂-adrenergic agents, methylxanthines and amrinone as discussed earlier, occur at concentrations of 30 to 1,000 µM. They are rapid in onset and last for 20 to 100 minutes.

The positive inotropic effect of sulmazole is not due to a direct stimulation of β-adrenoceptors, a release of endogenous catecholamines, or an interaction with the cardiac glycoside receptor. Instead, the effect of sulmazole also resembles largely the effects of the classic methylxanthines, caffeine and theophylline. For instance, the drug produces contractures and prolongs the contraction at high concentrations; it inhibits phosphodiesterase activity and potentiates the positive inotropic effects of noradrenaline. This supports the existence of a causal relation between the positive inotropic effect, inhibition of phosphodiesterase and an increase in cAMP level. However, it should be pointed out that the positive inotropic effect of sulmazole appears not to be due solely to inhibition of phosphodiesterase. It has been shown experimentally that the drug in a therapeutic concentration (350 µM) increases the Ca²⁺ sensitivity of the contractile proteins (41), an effect that might contribute to the positive inotropic action of the drug. Herzig et al. (41) emphasized that sulmazole would be the first example where a change in Ca²⁺ sensitivity of the myofilaments contributes to the positive inotropic effect of a cardiotimulatory agent. However, whether or not this effect is unique is still a matter of debate, as discussed earlier in the case of the methylxanthines. But it should be noted that in the study of Herzig et al. (41), theophylline or caffeine in concentrations of up to 10 mM and amrinone in concentrations of up to 350 µM failed to produce any effect on the Ca²⁺ sensitivity of the contractile proteins.

Conclusions. This brief review has attempted to classify various old and new positive inotropic drugs according to their mechanisms of action. The major effects involved are summarized in Table 1. The inotropic properties of many of the agents discussed are related to an increase in myocardial cAMP levels, although these are brought about by different mechanisms. This is important as an increase in cAMP may potentially lead to tachyarrhythmias. Among the new inotropic agents, no drug appears to provide major advantages. The potential development of tolerance during chronic treatment and the occurrence and significance of possible side effects appear to be the most significant unresolved questions.

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