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POSITIVE INOTROPIC AGENTS

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INTRODUCTION

A large number of naturally occurring and synthetically prepared chemical agents produce a positive inotropic effect on the heart. Analogues of these compounds have been isolated, prepared, and tested, and a number of them also have positive inotropic effects (see Tables 1–6). A number of reviews on inotropic agents and their possible mechanisms have been published (1–7).

Because of space limitations, only compounds that have had extensive pharmacological investigation will be discussed here. Thus, we will consider newer adrenergic agents, new phosphodiesterase inhibitors, some polypeptides, and a number of miscellaneous compounds that have interesting pharmacological properties. The choice of compounds to be discussed was based on the interests of the authors; our readers may disagree with these choices.

THE ADRENERGIC AGENTS

There are three major actions of the effects of adrenergic agents on the heart: the inotropic, chronotropic, and arrhythmogenic effects. Adrenoceptors have been classified into α and β receptors (8) and subgroups of these (α 1, 2, and β 1, 2) have been postulated (9–11). The β-receptor is the one primarily responsible for inotropic and chronotropic effects, with the β-mediated inotropic effects most likely involving adenosine, 3'5'-cyclic phosphate (cyclic AMP) formation (12, 13). However, positive inotropic responses in heart muscle of various species, including man, can also be elicited by the activation of α receptors.

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This effect is usually demonstrated in cardiac muscle exposed to β-blocking agents. Here, an α-blocking agent will shift the dose response curve of epinephrine to the right. α-Activators are dopamine, epinephrine, norepinephrine, phenylephrine, methoxamine, and related substances (14). In low concentrations (up to 10 μM), the effects of phenylephrine are mostly α effects, while at higher concentrations both β and α effects are involved.

α-Adrenergic effects differ from those of β-mediated effects in having only a weak chronotropic effect and in not increasing cyclic AMP content of the heart. The time to peak tension and relaxation time are not changed by these adrenergic agents and, in contrast to β-adrenergic stimulation, the α activators do not increase cardiac irregularities and may even inhibit arrhythmogenesis (13b).

Although epinephrine (EP), norepinephrine (NE), and isoproterenol (IPN) have powerful positive inotropic effects, their usefulness in the therapy of heart failure has been limited by their poor gastrointestinal absorption and their positive chronotropic and arrhythmogenic properties. These disadvantages have prompted the search for orally effective adrenergic agents whose chronotropic, inotropic, and arrhythmogenic effects can be separated.

Separation of Inotropic and Chronotropic Effects

The separation of inotropic and chronotropic effects has been claimed for a number of adrenergic agents, such as dopamine, dobutamine and prenalterol. In general, this separation of effects is most evident in the intact animal. With dopamine, the differential effects are reduced or eliminated after reserpine treatment of the heart, thus suggesting that reflex phenomena contribute to this separation. With dobutamine, the differential effects on contractility and heart rate persist after adrenergic depletion (15, 16, 17). However, when isolated atrial and ventricular tissues are exposed to dobutamine, the heart-rate changes are more sensitive to dobutamine than are the inotropic changes (15, 17). Both pharmacological and ligand binding studies (18–23) show the existence of β-1 and -2 receptors in cardiac muscle. Furthermore, Hedberg et al (24) report that cat- and guinea-pig atria contain 75% β-1 and 25% β-2 receptors, while the ventricles contain mostly the β-2 receptor. These findings have been the basis for explaining the differential effects of an adrenergic agent on heart rate (β-2) and contractile force (β-1). However, Kenakin (25) and Kenakin & Beek (26) have not been able to demonstrate any selectivity for β adrenergic receptors with either dobutamine or prenalterol. Their findings agree with the studies of Bodem et al (15) and Lumley et al (17), which demonstrate no separation of inotropic and chronotropic effects in isolated auricular tissue. Thus, the differential effects of these agents on heart rate and contractility are very likely characteristics of the heart in situ. Levy & de Oliveira (27) have observed that the blood supply to ventricular muscle is greater than to the atrium, which

contains the sinus node. Potter et al (28) have shown that administered catecholamines are retained to the highest degree in those regions of the heart where blood supply is highest. Thus, the retention of H^3 NE per gram of tissue was about 8.4 times greater in the left ventricular, as compared with right atrial, tissue of normal dogs. This is an unexpected finding, since atrial tissue contains larger amounts of adrenergic nerve endings than do the ventricles. The left ventricle received the largest, while the right atrium (and possibly the sinus node) received the smallest amount of NE per unit of weight of cardiac tissue. If one considers that the amounts per gram of tissue thus received are going to be diluted in an equal amount of extracellular space, the concentration of an adrenergic agent would be higher at the ventricular cell surfaces than at the sinus node cells. This would be compatible with the observations that adrenergic agents, when given only in vivo, show this preferential effect on the contractility of the ventricle. The claims purporting preferential effects on contractile force of some of the adrenergic agents are thus best explained by vascular distribution of the injected material and the secondary effects on heart rate resulting from reflex changes caused by these agents. However, in the intact animal, differences in responses between substances with high intrinsic activity (NE) and those with relatively low intrinsic activity (dobutamine, prenalterol) are still apparent. Thus, at doses that produced an equal contractile response, NE and isoproterenol produced a greater increase in heart rate than dopamine, dobutamine, or prenalterol (16, 29, 30). Studies in isolated cat tissue show that equipotent chronotropic doses of NE, EP, IPN, dobutamine, and dopamine produce an equal increase in the contractile response in both auricular and papillary muscle (A. A. Alousi, unpublished data). It is thus likely that the differences between adrenergic agents observed in the intact animal are due to pharmacological differences on vascular smooth muscle, reflex effects, and intrinsic adrenergic blocking actions of a drug (26).

Loss of Cardiac Activity of Adrenergic Agents Following Prolonged Administration

Adrenergic-agonist desensitization of the contractile response and the increase in cyclic AMP content of intact heart muscle has been demonstrated by a large number of investigators (31). All these studies reported that either the chronic administration of an adrenergic agonist or procedures that increase sympathetic activity will cause a reduction in the responsiveness of the heart to an adrenergic β-agonist. Similar findings have been reported in human patients treated with dobutamine (32–35).

In asthmatic patients Galant et al (36) have shown that prolonged therapy with terbutaline, ephedrine, or metaproterenol produces, in polymorphonuclear leukocytes, a reduction in the binding sites of dihydroalprenalol and a reduction in the adenylate cyclase response. However, this reduction probably

does not represent desensitization in the bronchial smooth muscle, since Jenne et al (33) could not detect any significant change in the responsiveness of patients to terbutaline in terms of vital capacity and airway resistance. Other parameters, such as decrease in diastolic blood pressure, increase in blood lactate, cyclic AMP, glucose, and lowering in the eosinophil count, show a significant desensitization (37).

Tohmeh et al (38) have shown that short-term infusion of isoproterenol in normal human subjects increased, while a longer infusion time (4–6 hours) decreased, adrenergic binding sites in mononuclear cells of these patients. In all the above situations, prolonged administration of adrenergic agents resulted in a reduction of the effects of the agonist on the heart and circulation but not in bronchial smooth muscle, although the drug concentration in blood seemed to be at a constant level. These data suggest that desensitization of blood constituent must be interpreted with caution, since the appearance of desensitization seems to vary from organ to organ.

Desensitization of tissues to the effects of adrenergic agents is a complex phenomenon that has been recently reviewed by Lefkowitz et al (39), Perkins et al (40), and Harden (31). This seems to involve changes in the coupling mechanism of the receptor to the adenylate cyclase system and a reduction in the number of binding sites, as well as a structural change in a protein moiety of the adrenergic receptor (31).

In some cell types, catecholamine refractoriness can be reduced or prevented by treating the cells with inhibitors of protein synthesis (41, 42), by adrenal cortical hormones, (43, 44, 45), and by quinacrine (46). Both adrenocortical hormones and quinacrine are inhibitors of phospholipase, phosphatidyl choline synthesis has been implicated in receptor affinity (47, 48), and prevention of adrenergic desensitization in rats by quinacrine has been reported by Torda et al (49) and Yamaguchi et al (50).

The appearance of desensitization of adrenoreceptors after prolonged exposure poses a serious practical problem, since both the cardiac inotropic and the vasodilator effects of these substances can be attenuated or lost with chronic administration.

DOPAMINE

Dopamine (see Table 1) is classified as a mixed amine since it produces positive inotropic and chronotropic effects by releasing NE from presynaptic membranes and by acting directly on both α and β receptors in the heart (16, 29).

Thus, dopamine increased the rate of discharge from the sinus node and ectopic foci. It shortened the duration of the action potential and the refractory period of cardiac muscle and increased excitability, automaticity, and contractility of the heart (51, 52).

Table 1 β-Adrenergic compounds that have inotropic effects (only main references are given)

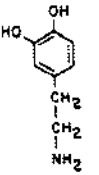
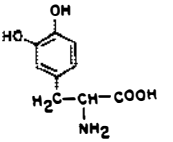
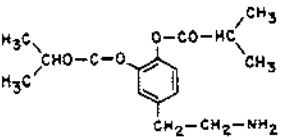
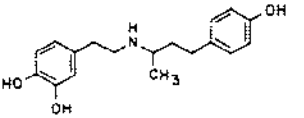
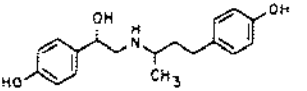
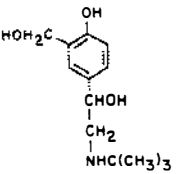
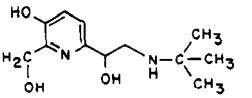
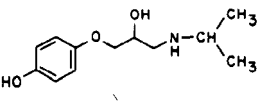
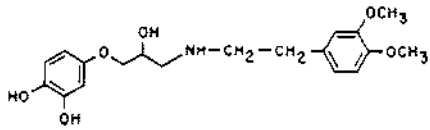
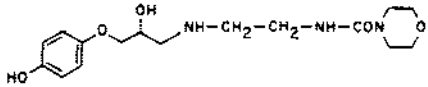
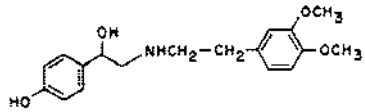
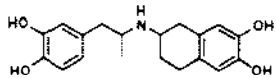
Name	Formula	References
Dopamine		29, 81, 134, 318
Levodopa		134, 319, 320
Ibopamine (SB 7505)		128, 130, 131, 134
Dobutamine		15–17, 77, 82, 92
Butopamine		90, 135a, 135b, 321
Salbutamol		136–138
Pirbuterol		34, 122, 124–126
Prenalterol H 133/22 or H 80/62		19, 113

Table 1 (*Continued*)

Name	Formula	References
RO 363		146, 147
ICI 118587		121
TA 064		142, 144
ASL 7022		322–324

The dopamine-induced inotropic and chronotropic responses are attenuated by the preadministration of cocaine (53), reserpine (54), and desmethylimipramine (16), and potentiated by monoamine oxidase inhibitors (55). β-Adrenergic blockers reduce or eliminate the effects of dopamine on automaticity and increase excitability of the heart (52). They only reduce the inotropic effects in species where both α and β adrenergic receptors have been demonstrated (56a, 56b). Thus, in the dog heart, which does not contain α receptors (57), the positive inotropic and chronotropic effects of dopamine are blocked by a β adrenergic antagonist (58). In frog, rat, guinea pig, rabbit, and human heart muscle, α and β receptors have been demonstrated (59a, 59b). In rabbit hearts, the addition of a β blocker will shift the dose-response curve of dopamine to the right and this curve can be further displaced to the right by the addition of an α adrenergic blocker (60–63). The stimulation of α receptors does not significantly affect heart rate in concentrations that cause positive inotropic effects (59a, 64). It does not influence automaticity or ectopic foci production and may actually inhibit cardiac arrhythmogenesis (52). The α-receptor effects on cardiac contractility are best demonstrated in the presence of a β blocker at low rates of stimulation, at low temperatures, and at low concentrations of the agonist. Under these conditions, an α blocker will further reduce the effects of EP and NE, but not of IPN (60, 65).

It is fairly well established that activation of β-adrenergic receptors in the heart can be correlated with an increase in the cyclic AMP content of myocardial tissue. α-Adrenergic stimulation does not increase the cyclic AMP concen-

tration. Dopamine increased the cyclic AMP content of rat and rabbit cardiac muscle (63, 66, 67); however, this increase was abolished by reserpine pretreatment, although the inotropic effect was reduced. This suggests that NE release is the causative agent of this dopamine effect. However, since dopamine stimulated both α as well as β receptors, one would expect dopamine to increase the cardiac concentration of cyclic AMP; however, no such increase has been observed (62, 68, 69). Huang & Drummond (70) have reported that α adrenoreceptor stimulation reduced the cyclic AMP response produced by isoprenaline. Furthermore, dopamine-induced increases in cardiac cyclic AMP are enhanced by the addition of an α blocking agent (63). The above findings thus suggest that α receptor activation can counteract the increase in cyclic AMP produced by stimulation of the β receptors.

All these findings suggest that dopamine effects on cardiac contractility are predominantly due to β adrenergic stimulation; however, α effects will be observed only under special experimental conditions, especially under those where β receptor activity is reduced. Thus, in hypothyroidism, where sensitivity to β adrenergic stimulation was reduced (71), the response to α receptor stimulation was actually increased (59a). This α adrenergic effect could thus contribute to the effects of dopamine and could be of advantage under hypothyroid shock or arrhythmogenic conditions.

In the intact dog, dopamine effects on cardiac contractility preceded the effects on heart rate. Tuttle & Mills (16) and Lumley et al (17) have shown that this inotropic selectivity is eliminated by pretreatment with adrenergic depleting agents, and in isolated auricular preparation Lumley et al (17) observed that dopamine is actually rate selective. One must conclude that in the intact dog this inotropic selectivity must be related to reflex adjustments, possibly α-adrenergic effects as well as the blood flow distribution effects discussed above. No dopaminergic receptors have been observed in cardiac muscle (72, 73). Thus, presynaptic effects of dopamine on cardiac function are probably not operative.

Dopamine increased the automaticity of the sinus node and ectopic foci and reduced the ventricular fibrillation threshold and the repolarization time of the action potential (52). Under cyclopropane anesthesia, both dopamine and NE produced arrhythmias and ventricular fibrillation, but dopamine had only 1/100 the potency of NE. The arrhythmogenic effects of dopamine were prevented by β-adrenergic blocking agents (52, 74).

Dopamine has been used clinically by the intravenous route for the treatment of shock and acute and chronic heart failure. However, dopamine's propensity to increase heart rate and its arrhythmogenic potential have required careful dose adjustment of this drug. In patients with congestive heart failure, dopamine increased cardiac output, but also increased pulmonary capillary wedge pressure and systemic blood pressure, possibly due to the α-adrenergic effects

on vascular smooth muscle; in addition, a vasodilator effect on renal blood vessels has been observed due to its activation of dopaminergic receptors in kidney blood vessels (29).

Dobutamine

Dobutamine has an asymmetric carbon atom attached to the amine group. With the β phenethylamines such as NE, asymmetry occurs in the β-carbon, and the (−)−isomer is about two log units more effective than the (+)−isomer for both the α and β receptors. Maximal effects for both isomers are the same (75). Thus, these isomers have the same "efficacy" but different "affinities" for the receptors. Recently, Kent et al (76) have shown that there are two interconvertible β binding sites for catecholamines on frog red cell membranes, namely, "high" and "low" affinity states. The ability of an agonist to activate the adenylate cyclase system (efficacy) seems to correlate with its ability to form the high affinity state with the receptor.

With dobutamine, the α effects are observed both with the (±)−, (+)− and (−)−isomers and both isomers bind to aortic tissue with equal affinities (77), although only the (−)−isomer is an agonist, while the (+)−isomer is an antagonist to the (−)−isomer of dobutamine as well as to phenylephrine. The β-adrenergic effects of the dobutamine isomers are the same since both produced positive inotropic and chronotropic effects, although, in contrast to the β-phenethylamines, the (+)−isomer of dobutamine has a greater activity (about 1 log unit) than the (−)−isomer. These results indicate that the stereochemical requirements of α- and β-adrenergic receptors are not the same. The asymmetry in the dobutamine molecule governs efficacy rather than affinity as regards the α receptor, while in the β-phenethylamine series, affinity rather than efficacy is governed by the asymmetry in the β carbon atom (77). The effects of the asymmetry in the dobutamine molecule influenced the affinity to the β receptor and had little effect on efficacy. These results indicate that the α- and β-adrenergic receptors have different steric requirements that determine efficacy and affinity of adrenergic agents. The asymmetry observed with dobutamine may be more important in determining efficacy and affinity properties at the β and α receptors than the β carbon asymmetry observed with the phenethylamines (77).

These differing effects of (+)− and (−)−isomers of dobutamine explain the complex actions of the mixed form used clinically.

Dobutamine is active intravenously but is poorly absorbed from the gastrointestinal tract and has a short half-life. It can be classified as an adrenergic agent with β_1-, β_2-, and α-adrenergic actions (25, 78). Its inotropic and chronotropic effects are blocked by β-blocking agents, and here its α effects manifest themselves by increases in blood pressure and peripheral vascular resistance. The β effects are best seen after the administration of an α blocking agent

(15–17, 77, 79, 80–82). Robie et al (80) compared the effects of dobutamine with NE. The dose of dobutamine that reduced femoral blood flow was 15 times the dose that increased femoral blood flow and was about 180 times the equieffective dose of NE. The effects on cardiac contractile force required 40 times the equieffective dose of NE.

In the intact vagotomized dog as well as in the dog treated with syrosingopine, a catecholamine depleter, dobutamine produces a dose-related increase in contractility with minimal increases in heart rate (16, 17, 82). Hinds & Hawthorne (83) administered dobutamine intravenously to instrumented dogs and, with infusion rates of 5–20 μg/kg/min, linear increments of a number of indices of cardiac contractility occurred without a change in left ventricular end diastolic pressure, mean arterial pressure, or heart rate. Similar effects have been observed with infusion rates of 0.1–0.2 μg/kg/min of INE; however, at any level of increased cardiac contractility, heart rate is higher with INE than with dobutamine (83). In dogs with acute myocardial ischemia, Kirlin et al (84), Willerson et al (85), Rude et al (86), and Liang et al (87) observed an increase in heart rate, myocardial contractility, and elevated ST segment of the electrocardiogram, although blood flow to the heart had increased and blood pressure had not changed. Dobutamine administration during coronary occlusion did not increase the area of injury unless doses of dobutamine were administered that substantially increased heart rate (87).

In dogs, Robie & Goldberg (79) and Vatner et al (82) compared dopamine and dobutamine and showed that dopamine increased renal blood flow but did not increase femoral flow; dobutamine, on the other hand, increased femoral blood flow without changing renal flow. In general, dobutamine favors redistribution of blood to muscle and coronary vessels over mesenteric and renal flow.

Bodem et al (15), Lumley et al (17), and Alousi (unpublished data) observed that in isolated preparations heart rate effects were more sensitive to dobutamine than were contractile force changes. Dobutamine increased the cyclic AMP content of the cat (88) and rat hearts (89). The increase in cyclic AMP preceded an increase in phosphorylase-a activity and dobutamine had approximately 1/45 the activity of INE (89).

Clinical studies have been reviewed by Goldberg et al (81), Leier et al (90), Plachetka (91), Sonnenblick et al (92), and Weber & Tuttle (93).

Dobutamine given intravenously to patients with heart failure increased cardiac output linearly with dose, decreased pulmonary capillary wedge pressure, and increased urinary sodium excretion with no significant increase in heart rate or tachyarrhythmias.

Willerson et al (85) and Vasu et al (94) have shown that dobutamine, like a number of other catecholamines, increased the oxygen consumption of the normal heart by augmenting heart rate and increasing ventricular wall tension.

However, in the failing heart, contractility was increased and the left ventricular end diastolic pressure was decreased, the net result being no change in oxygen consumption and an increase in the efficiency of the heart.

When dobutamine was compared with dopamine in low output heart failure, both drugs had approximately equivalent effects on the various indices of positive inotropism and heart rate (91, 95–97). Dopamine increased blood pressure and left ventricular end diastolic pressure, while dobutamine decreased both parameters.

Most of these clinical studies with dobutamine have lasted 24–48 hours. Unverferth et al (32) observed that the cardiac effects of dobutamine in patients were significantly reduced after 96 hours of constant administration. This suggests that with dobutamine desensitization of the heart was occurring, thus limiting the use of this drug to acute situations.

Unverferth et al (32) and Leier et al (98) reported that both symptomatic and hemodynamic improvement persisted for a week in 68% of the patients following discontinuation of three-day therapy with dobutamine. Similar observations have been made with the cardiotonic agent amrinone (99), where the beneficial effects on cardiac function persisted for days or even weeks after drug therapy was stopped and blood concentration of the drug had been dissipated. Very few studies on this aspect of cardiac pharmacology have been published, but the development of an endomyocardial biopsy technique (100, 101) makes it possible to do histological as well as biochemical studies with human heart tissue. Unverferth et al (32) have obtained cardiac tissue from heart failure patients after dobutamine therapy. By means of electron microscope techniques, they made quantitative ultrastructural analysis of these biopsy samples. Simple bed rest had no significant effect on the crista-to-matrix ratio of mitochondria, the size of the mitochondria, or the number of electron-dense particles per mitochondrion. Those patients who had a good clinical response to dobutamine therapy showed a decrease in both the size of the mitochondria and the crista-to-matrix ratio, as well as a decrease in the number of the electron-dense particles in mitochondria. The electron-dense particles are seen in degenerating or ischemic cells (102–104) and cells from failing hearts from hamsters and dogs frequently show the appearance of these dense particles, mitochondrial enlargement, and the change in crista-to-matrix ratio (105, 106). These phenomena indicate an improvement in the physical integrity of mitochondria and possibly mitochondrial function. The mechanism by which dobutamine causes this return toward a normal state of mitochondrial structure is not understood; however, dobutamine and other cardioactive agents produce cardiac blood flow and biochemical changes, which in turn could trigger the repair process in cardiac cells, especially those cells situated at the borderline area of an ischemic zone. This is obviously an important area of cardiac pharmacology and more data should become available in the future.

Prenalterol

Prenalterol (see Table 1) is an orally active β-adrenergic agent (107). In the intact dog, prenalterol produced a positive inotropic effect at dosages that did not increase heart rate, and Carlsson et al (19), Manders et al (30), Strossberg & Montgomery (108), and Williams (109) have attributed this to a selective effect on the β_1 adrenoreceptor. However, binding studies (110, 111) do not support this viewpoint. Studies in isolated cardiac tissue by Kenakin et al (26, 112) have shown that prenalterol does not have positive inotropic selectivity. In coronary arteries and other tissues with β_2 receptors, prenalterol acted as a β blocker (26, 78).

Thus, the in vivo selectivity of prenalterol for inotropic over chronotropic effects cannot be related to receptor binding mechanisms and is most likely due to reflex mechanisms that are initiated when the drug is administered to the intact animal. This is probably due to distribution of the drug in ventricular and auricular tissue and the β-blocking action of this drug. Heart rate and contractility dose-response curves are shifted equally to the right following the administration of a β-blocking agent (113). In intact animals prenalterol produces a greater increase in contractile force than isoprenaline or terbutaline when compared at doses that produce an equal chronotropic effect. Prenalterol doses that produce an inotropic response do not provoke or potentiate cardiac arrhythmias (19).

In man, prenalterol has an elimination half-life of a few minutes, with both fast and slow components. On oral administration, bioavailability was about 25% and elimination half-life was 1.2–1.7 hour. A slow-release form of the drug, which produced effective plasma concentrations for a period of 10 hours, allowed twice daily administration (114).

Prenalterol, when given either intravenously (0.13–0.5 mg) or orally (2.5–10 mg) to humans, increased heart rate, systolic blood pressure, and pulse pressure with either no significant change or a reduction in diastolic pressure (114–116). The above dosages of prenalterol had little effect on renal plasma flow and glomerular filtration rate (117) and had no demonstrable effect on bronchial smooth muscle (118).

A number of clinical studies in post-ischemic heart failure have shown that intravenous and oral administration of prenalterol caused an enhancement of left ventricular function. In some of these studies, increased ectopic activity and ventricular tachycardia were observed (72, 119). The maximum rate of pressure fall (peak negative dp/dt) also increased, suggesting improved relaxation of the stiff ventricle (120).

From the available data, it is not possible to assess the usefulness of this drug following chronic administration. However, experience with other β-adrenergic agents has been disappointing because of the occurrence of the desensitization phenomenon. Kenakin & Beek (26) have shown that in vitro

desensitization of guinea pig atria to isoproterenol eliminates the agonist activity of prenalterol. These findings suggest that prolonged therapy with prenalterol could result in desensitization, thus limiting the usefulness of this drug to the treatment of acute heart failure.

ICI 118587

This compound, an analog of prenalterol, is a partial agonist and also has β antagonist properties (121).

Pirbuterol

Pirbuterol is an orally active catecholamine related to salbutamol, which has both β_1 and β_2 effects. It has been studied in both animals and human patients with heart failure. Van Arman et al (122), Moore et al (123), and Constantine et al (124) have described the animal pharmacology of pirbuterol. The data of Gold & Horowitz (125) show that in the unanesthetized instrumented dog, pirbuterol produced equivalent increases in heart rate and cardiac contractile force. Left ventricular end diastolic and systolic volumes were decreased, while left ventricular stroke volume was not changed significantly (0.125–8 μg/kg/min). In those preparations where heart rate was kept constant by pacing, left ventricular end diastolic volume did not change except at the highest rates of pirbuterol infusion, indicating that heart rate changes had contributed to these effects. β blockade shifted the dose-response curve to the right. The heart rate selectivity of pirbuterol in cardiac muscle is not very striking and in this respect the drug resembles isoproterenol.

Clinical findings in heart failure patients have shown that pirbuterol induced both vasodilatation (126) and inotropic effects (127). Due to the symptoms of tremor and nervousness, the dose of pirbuterol was limited to 20 mg three times daily. Exercise tolerance, maximum oxygen uptake, and left ventricular diameters were measured, and after four and seven weeks of therapy, pirbuterol had no demonstrable effects over placebo.

In a similar study, Colucci et al (34) observed a marked attenuation of the hemodynamic effects of pirbuterol in patients. This was correlated with the down regulation of β receptor ligand binding by lymphocytes obtained from these patients. Thus, pirbuterol, like a number of other adrenergic agents, shows evidence of attenuation of its positive inotropic effects, possibly because of reduced binding of the agonist to the β receptors of the heart.

Ibopamine

Ibopamine (see Table 1) is a di-ester of N-methyl dopamine that was synthesized as a renal vasodilator and diuretic. In dogs, oral administration of ibopamine increased renal blood flow with no other observable cardiovascular effect. Large doses also increased femoral blood flow and left ventricular

pressure and its rate of increase, dp/dt, as well as systolic and diastolic arterial pressure. These effects are reminiscent of the effects of dopamine, except that ibopamine had much longer-lasting activity and was orally effective. In rats, oral ibopamine increased urinary sodium without affecting potassium excretion. No central nervous system effects were observed (128).

Ibopamine increased the contractility of isolated guinea-pig papillary muscle (129).

In humans, oral ibopamine produced a decrease in systolic time intervals and a diuretic effect (129–134).

In patients with cardiac failure, ibopamine given orally increased cardiac index and stroke volume without significant changes in heart rate or blood pressure. Both pulmonary arterial pressure and systemic vascular resistance were decreased and these effects lasted for 5–7 hours (129). The effects of prolonged administration and its arrhythmogenic potential have not to our knowledge been assessed.

Butopamine

Butopamine (see Table 1) was prepared by Tuttle et al (unpublished data) and has a structure similar to dobutamine. This compound is refractory to the action of catechol-O-methyl transferase and thus it is orally active and has a long-lasting action. Clinical findings in acute heart failure cases have been reported by Thompson et al (135). Intravenous administration produced an increase in the cardiac index and heart rate and shortening of systolic time intervals. A few patients experienced ventricular ectopy, especially with the higher doses used. No data pertaining to oral administration are available.

Salbutamol

Salbutamol (see Table 1) was developed as an oral bronchodilator because of its marked β_2-adrenergic activity on bronchial smooth muscle. The compound has positive inotropic and chronotropic effects on the heart and in heart failure in man it improved all cardiac ventricular parameters and produced only a moderate increase in heart rate (136–138). No data on the chronic use of this drug are available.

Doxaminol (BM 10 1088)

Doxaminol is an orally effective β sympathomimetic agent. In intact animals, it had a positive inotropic selectivity over chronotropic activity, with minimal effects on blood pressure. In combination experiments, the inotropic effects of doxaminol were additive to those of digitoxin without an increase in cardiac arrhythmias (139). Acute clinical studies in normal subjects (140) and heart failure patients (141) have essentially confirmed the animal data. No data for prolonged use of this drug in heart failure patients have been

reported, nor are data available to exclude an action by a release mechanism of NE.

TAO64

TAO64 (see Table 1) is an orally effective adrenergic agent. In dogs, Nagao et al (142) and Ikeo et al (143) have shown a separation of inotropic and chronotropic effects. In heart failure patients, Kino et al (144) observed that TAO64, after intravenous and oral administration, produced increases in cardiac output, dp/dt, a reduction in the left ventricular end diastolic pressure, and minimal changes in heart rate. This is another β-adrenergic agent with inotropic selectivity. No chronic use studies in human heart failure patients have come to our attention.

ASL-7022

ASL-7022 (see Table 1) is a tetrahydronaphthalene compound. In dogs it has β-adrenergic properties on cardiac contractility with a slight reduction in heart rate and blood pressure. Experiments in reserpinized dogs have not been reported and it is not clear whether this drug has direct β effects on heart muscle. No clinical data are available to us.

Abbott-47844

Abbott-47844 is a dopamine derivative that has prolonged renal vasodilator and diuretic effects that are not blocked by α- or β-blocking agents.

In larger doses, it had typical β-adrenergic effects on the heart of anesthetized dogs (145).

RO 363

RO 363 (see Table 1), a compound related to prenalterol, was synthesized with the claim that it had β_1 selectivity for adrenoreceptors. Animal studies by Iakovidis et al (146) and Raper et al (147) have shown that RO 363 is about half as active as isoproterenol as an inotropic agent on the heart. No experimental data in intact animals or human patients are available to us.

Bufuralol and Analogs

These benzofuranylethanolamine derivatives have both β-adrenergic activities when tested in anesthetized reserpinized and vagotomized cats. The compounds have no peripheral dilator action and have the expected inotropic and chronotropic effects on the heart (148, 149).

D4975

D4975 is a theophylline dopamine derivative about 100 times more potent than dopamine on heart rate and its effects are difficult to wash out (150). In

anesthetized cats, this compound increased cardiac contractile force in a dose of 0.5–1 μg/kg, which had none or only minimal chronotropic effects. It had about five times the activity of dopamine or dobutamine on the heart and had prolonged activity. Propranolol caused a partial antagonism of the cardiac effects of this compound.

The results indicate that D4975's actions on the heart involve both β-adrenoreceptor stimulation and phosphodiesterase inhibition (151). No clinical studies have come to our attention.

Adrenergic Transmitter-Releasing Agents

A large number of substances of varied chemical structure can release NE from sympathetic nerve endings (13, 152). The actions of these substances on the heart are in general similar to those observed with NE. A few of the more recently studied compounds, some of which have mixed actions (inhibition of phosphodiesterase), are listed in Table 2. All these compounds would have limited use in the therapy of heart failure because of their propensity to increase peripheral resistance and because they would be relatively ineffective in the treatment of severe heart failure where the NE content of the heart is reduced.

PHOSPHODIESTERASE (PDE) INHIBITORS

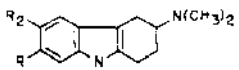
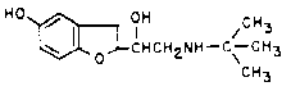
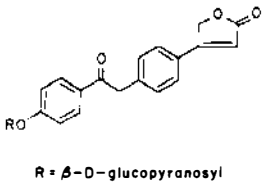
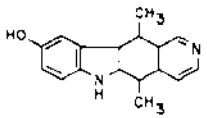
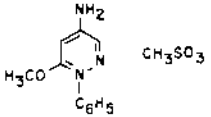
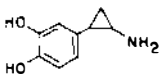
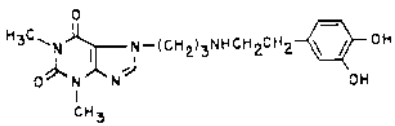
In recent years, interest in phosphodiesterase inhibitors (see Table 3) as inotropic and chronotropic agents has been revived. Much of our information on the action of these agents is based on studies with the methylxanthines, which affect cardiac, skeletal and smooth muscle, as well as the central nervous system and secretory functions.

Three possible mechanisms of action have been considered for the cardiac effects of the methylxanthines: (*a*) translocation of intracellular calcium; (*b*) increased concentrations of cyclic AMP resulting from the ability of these compounds to inhibit cyclic AMP phosphodiesterase and concomitant phosphorylation of membrane protein; (*c*) the ability of the methylxanthines to block adenosine receptors (13b, 153, 154).

As Scholz (13b) and Blinks et al (155) have reported, the methylxanthines in high concentrations produce an array of complex effects on cardiac muscle that defy a simple explanation. In the presence of methylxanthines, the active state is prolonged and intensified. The prolongation of the active state induced by caffeine is antagonized by procaine, while the intensity is not changed. The abbreviation of the contraction produced by catecholamines is blocked by caffeine, although the frequency induced abbreviation is not changed.

From the above findings, Blinks et al (155) postulated that the methylxanthines exert effects on cardiac excitation-contraction coupling by the inhibition of calcium uptake by the sarcoplasmic reticulum and increased calcium influx

Table 2 Compounds that cause the release of norepinephrine in cardiac muscle

Name	Formula	References
Aminotetrahydrocarbazole		172, 325
Benzofuranylethanol amine		148
AP10	 R = β-D-glucopyranosyl	326
9 Hydroxyelliptisine		327
Ameziniumetil sulfate (LU1631)		328–331
Dopamine analog (E) and (Z)-2-(3, 4-dihydroxyphenyl) cyclopropylamine hydrochlorides		324
Theophylline-dopamine derivative		150, 151
Prolactin	Molecular weight 22,500	332–334

through the sarcolemmal membrane. From recent studies, Blinks et al (156, 157) have concluded that the changes in aequorin light signals obtained from cardiac muscle indicate changes in the amount of intracellular calcium in response to the action potential. The decline of the light signal is probably due

Table 3 Phosphodiesterase inhibitors

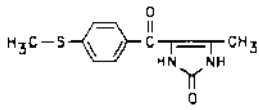
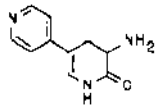
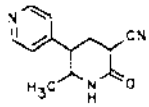
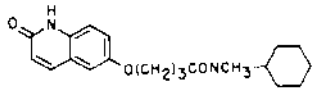
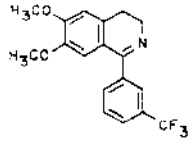
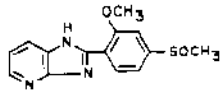
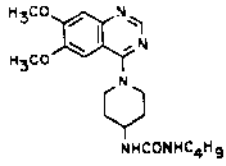
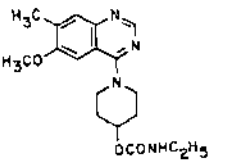
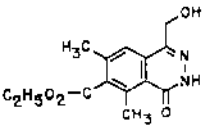
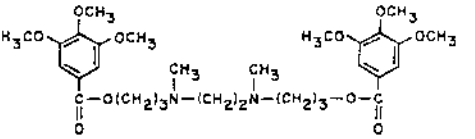
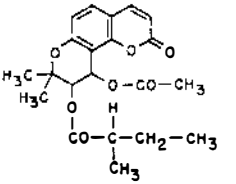
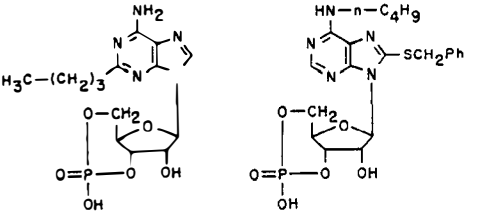
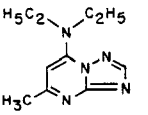
Name	Formula	References
MDL 17043 1,3-dihydro-4-methyl-(5-[4-(methylthio)benzoyl]-2H-imidazol-2-one		206, 207, 211, 213, 215, 216
Amrinone (Win 40680)		172, 173, 191–192b, 195, 335, 336
Milrinone (Win 47203)		198–200b, 337, 338
Cilostamide OPC 3689		232, 233
USV 2776 6,7-Dimethoxy-1-[3(trifluoromethyl) phenyl]-3, 4, dihydroisoquinoline HCl		339
Vardax Sulmazole ARL115 BS		220a, 225a, 225b, 340
Buquineran UK 14275		226, 230, 231

Table 3 *(Continued)*

Name	Formula	References
Carbazeran UK 31557		
Phthalazinol		234, 341
Ustimon		342
Visnadin		343
Analogs of Cyclic AMP		310, 311, 344
Trapidil Trapyrin Rocornal		345–347

to the binding of calcium to troponin C, the sarcoplasmic reticulum, and other calcium binding sites. The binding of calcium to the sarcoplasmic reticulum is related to the formation of cyclic AMP and the phosphorylation of phospholamban and sarcolemmal proteins. Rall & West (158) and others (13b) observed that methylxanthines potentiated the effects of a catecholamine in isolated heart

muscle, probably due to the inhibition of cyclic AMP phosphodiesterase. The prolonged active state following administration of a methylxanthine was accompanied by a proportional prolongation of the aequorin light signal. The height of the aequorin light signal is not increased by methylxanthines; however, its duration is prolonged and its rate of rise is decreased (157), suggesting that calcium release and uptake are inhibited. Another possible mechanism of methylxanthines has been discussed by Fabiato & Fabiato (159), Guthrie & Naylor (160), and Endoh & Kitazawa (161), who have observed a caffeine-induced increase in calcium sensitivity of skinned muscle. They suggest that sensitization of the contractile mechanism of heart muscle by the methylxanthines is another mechanism of action of phosphodiesterase inhibitors.

Stimulation of the contractility of isolated cardiac papillary muscle requires a concentration of 0.5–1.0 μg of theophylline per ml of bathing fluid (2.5–5.0 μM) (162). Shifting the dose response curve of NE requires about 10^{-4} M (18 γ/ml) theophylline (158). The latter effect may be due to an increased concentration of cyclic AMP. Minimal inhibition of phosphodiesterase requires about 50 μM of theophylline, which is about 50 times the dose that produced a detectable increase in cardiac contractile force in isolated cardiac muscle. This is inconsistent with the concept that the methylxanthines produce a positive inotropic effect in heart muscle by inhibiting cyclic AMP phosphodiesterase (163); however, such inhibition of phosphodiesterase may be of importance when high concentrations of theophylline (above 10^{-4} M) are used (164).

It is well known that adenosine induces a receptor-mediated inhibition of cardiac adenylate cyclase (165, 166). Contraction of cardiac muscle is inhibited by adenosine and partially reversed by a catecholamine or methylxanthines (167, 168). In cardiac muscle, adenosine is bound to the crude microsomal fraction (169). The binding of adenosine to the microsomal fraction satisfies the criteria for membrane binding and this binding was inhibited by ATP, ADP, AMP, and cyclic AMP (166, 170). Guthrie & Nayler (160) reported that caffeine inhibits the adenosine-induced reduction of Ca^{++} uptake by cardiac muscle. It is thus possible that the methylxanthines could act on cardiac contractility by a mechanism related to adenosine regulation of cardiac contractility as well as cardiac cyclic AMP (154, 163).

Specific antagonists to adenosine may have greater organ and tissue selectivity than the methylxanthines and future work in this area of pharmacology may well lead to more specific therapeutic agents than the methylxanthines, as well as to a better understanding of the mechanism of action of the older and newer drugs.

Cardioactive Bipyridines

The cardioactive bipyridines are a new chemical entity with both positive inotropic and vasodilatory activity (171, 172).

Amrinone—Inocor®

EFFECTS ON THE HEART Amrinone, 5 amino-[3,4'-bipyridine]-6-one (see Table 3), is a positive inotropic agent with vasodilatory properties. A concentration-dependent (3–1000 γ/ml) positive inotropic effect was demonstrated in isolated atrial and/or ventricular tissues of cats, dogs, rabbits, guinea pigs, monkeys, and humans (173–184).

In isolated and failing hearts, amrinone caused significant increases in cardiac contractile force, coronary blood flow, oxygen uptake, and total cardiac work with no significant changes in heart rate and an increase in the efficiency of the heart (175, 185).

The in vivo inotropic activity of amrinone was observed in anesthetized and unanesthetized dogs (173, 185). In intravenous doses of 0.1–1.0 mg/kg or oral doses of 2–10 mg/kg, amrinone caused significant positive inotropic effects, a reduction in peripheral resistance, and no significant effect on heart rate or blood pressure. Higher doses of amrinone further increased contractile force, decreased systolic and diastolic blood pressure, and increased heart rate with no deleterious changes in the ECG (173, 186).

EFFECTS ON BLOOD VESSELS The vasodilatory properties of amrinone were observed in denervated, isolated, hind-limb preparation (173). Amrinone caused relaxation of untreated or KCl-constricted, isolated, procine coronary arteries (187), norepinephrine- or KCl-constricted, isolated rabbit aorta (168), and phenylephrine-constricted pulmonary arteries (189) and bronchial smooth muscle (190).

Clinical trials with amrinone were conducted in patients with severe congestive heart failure (New York Heart Association Functional Classes III and IV) refractory to conventional therapy. All patients were on digitalis and diuretics; some were on antiarrhythmic and vasodilator agents.

Short-term therapy with intravenous amrinone (bolus injections of 0.50–2.5 mg/kg) showed dose-related improvement in cardiac index with reduction in pulmonary capillary wedge pressure, right atrial pressure (20 to 50%), and no change in heart rate and mean arterial pressure (191, 192a, 192b, 193). Long-term therapy (up to three years) with oral amrinone (100–300 mg, t.i.d.) caused similar improvement in cardiac performance and increased exercise tolerance (194, 195, 196). In patients with ischemic cardiomyopathy, Benotti et al (197) demonstrated beneficial hemodynamic changes, without an increase in myocardial oxygen consumption.

SIDE EFFECTS OF AMRINONE Of the more than 500 patients treated with amrinone, approximately 15% have demonstrated dose-related, reversible platelet count reduction. A similar number have complained of gastrointestinal

disturbances that required dose adjustment or discontinuation of therapy (193, 194, 196). Hepatic enzyme abnormalities and arrhythmias have also been reported.

Milrinone

Milrinone (Win 47203) (see Table 3) is 1,6-dihydro-2-methyl-6-oxo-[3,4-bipyridine]-5-carbonitrile; it is 20–50 times more potent than amrinone (184, 198a, 198b, 199). The pharmacological profile of milrinone is probably similar to amrinone in all test systems, including patients with congestive heart failure. So far, milrinone has been tested in more than 200 subjects and patients using intravenous and oral regimens (200a, 200b, 201). In exploratory efficacy studies in patients with severe congestive heart failure (Classes III and IV), the beneficial effects of milrinone were observed for several months and were not accompanied by any of the side effects observed with amrinone (200b, 201).

Mechanism of Action of the Cardioactive Bipyridines

Both amrinone and milrinone are phosphodiesterase inhibitors; however, it is by no means clear whether this effect is responsible for the inotropic properties of these compounds. Both compounds increase the cyclic AMP content of cardiac muscle; however, here again it is not clear whether this effect is the only mechanism responsible for the inotropic actions of the bipyridines (179, 181, 198a, 198b). The inotropic and chronotropic effects of amrinone are not blocked by α- or β-adrenergic blocking agents, by H_1 or H_2 histamine blocking agents, or by inhibitors of prostaglandin synthesis. The bipyridines do not inhibit cardiac Na^+,K^+-activated ATPase (173, 198a, 198b, 203). A number of investigators have observed that amrinone and milrinone increase calcium uptake in a variety of cells, including heart cells (189, 203, 204). Morgan et al (205) studied the effects of amrinone on the aequorin light signal in cardiac muscle. Amrinone increased the amplitude of both the force of contraction and the light signal, increased the time to peak response, and increased the rate of decline of the light signal. This suggested that amrinone increases both the intracellular Ca^{2+} concentration and the rate of Ca^{++} sequestration to the contractile proteins. Milrinone has a biphasic dose response curve in dog ventricular trabeculae, which suggests the possibility of more than one mechanism of action (A. Farah & P. Canniff, unpublished data), possibly one on Ca^{++} uptake and one due to formation of cyclic AMP and its effects on Ca^{++} uptake and release.

MDL 17043

MDL 17043 (see Table 3) is a phosphodiesterase inhibitor with inotropic, chronotropic, and vasodilator properties (206, 207). Synthesis of this compound was described by Schnettler et al (208). It is active by the intravenous

and oral route and, after an oral dose (30 mg/kg) in dogs, its inotropic effect reached a maximum in 30 minutes and lasted about 4–5 hours (207). MDL 17043 is eliminated by biphasic mechanisms and after 3 mg/kg the half-life can be estimated to be about one hour (209). In dogs, it shortened both the QT interval and the atrioventricular conduction time but had no effect on the action potential duration (212).

Similar to other PDE inhibitors, this drug produced positive inotropic effects that are not blocked by α- or β-adrenergic blockers, by H_1 and H_2 blockers, by cardiac denervation, or by reserpine pretreatment (206). MDL 17043 has little effect on cyclic AMP phosphodiesterase I and II activity, but phosphodiesterase III was strongly inhibited by a partially competitive mechanism and 50% inhibition required 1.3 μM, which was only 1/15 the dose required for amrinone (211). However, the in vitro and in vivo effects of MDL and amrinone are about the same, thus suggesting that PDE inhibition may not be the basic mechanism of action of so-called PDE inhibitors. MDL 17043 had minimal effect on dog kidney Na^+K^+ ATPase or on Ca^{++} ATPase obtained from cardiac sarcoplasmic reticulum. Calcium uptake by oxalate-supported cardiac sarcoplasmic reticulum was not changed by MDL 17043 concentrations that produced inotropic effects. In experimental preparations, MDL 17043 had rather similar pharmacological properties to amrinone.

Only limited data on the clinical efficacy of MDL 17043 has so far been published. In normal humans, Belz et al (212) administered the compound either intravenously or orally in a dose of 1–3 mg/kg. These amounts produced cardiac inotropic effects as measured by systolic time intervals and the effects of the drug lasted for more than four hours. Absolute bioavailability was about 60%. In heart failure cases Crawford et al (213), Uretzky et al (214, 215), and Ferry et al (216) have observed with intervenous MDL 17043 (maximum dose 3 mg/kg) an increase in cardiac output and dp/dt, a reduction in the pulmonary capillary wedge pressure, and total peripheral resistance with no arrhythmogenic effects. No data on chronic use of this drug have come to our attention. More recently, Petein et al (217) have published data on the clinical effectiveness of another imidazole derivative (MDL 19205) with results similar to those seen with MDL 17043.

(AR-L115 BS) Vardax, Sulmazole

Vardax (see Table 3) is one of a large series of benzimidazoles synthesized by Amstel & Kutter (218). Following preliminary screening AR-L115 BS was chosen for further development (219).

AR-L115 BS is a phosphodiesterase inhibitor with a K_i of about 315 (K_i of papaverine = 7.9) and at similar concentrations it produced maximal effects on cardiac contractile force in guinea-pig atria. Neither myocardial adenylate cyclase nor cyclic AMP content was changed by this drug. The pharmacology

and pharmacokinetics of AR-L115 have been summarized (219) and the data show that AR-L115 is an effective inotropic agent with vasodilator properties. In a dosage that increased cardiac contractility it did not increase heart rate. However, with higher doses, blood pressure was decreased and heart rate was increased.

In the earlier reports, Dahmen & Greeff (220) have claimed that neither pretreatment with reserpine nor β-adrenergic agents reduced the inotropic effect of AR-L115 in guinea-pig auricular muscle. However, Petein et al (221) have shown that AR-L115 increased the release of NE from dog heart. Brutsaert et al (222) have shown that β-adrenergic blocking agents markedly reduced the effects of AR-L115 in rat cardiac tissue and Pouleur et al (223) and Verdouw et al (224) observed a reduction by a β blocker of the inotropic effect of AR-L115 in intact dogs and humans. It is thus likely that this compound, although a phosphodiesterase inhibitor, produced its positive inotropic effect by a second mechanism, namely, release of NE.

The clinical data in man show that AR-L115 has both cardiotonic and vasodilator properties following intravenous and oral administration. However, in cases with severe heart failure, the effects on cardiac output were frequently quite modest, possibly because of the low NE content of the heart observed in severe heart failure. In angina patients AR-L115 improved both hemodynamics and the symptoms of angina (225a, 225b).

No data on prolonged use of AR-L115 in heart failure cases have been reported.

Buquineran (UK 14275)

Buquineran (see Table 3) is a piperidine derivative that inhibits cyclic AMP phosphodiesterase. It also causes the release of NE and its effects on isolated organs and intact animals are reduced by pretreatment with reserpine or a β-adrenergic blocker (210, 226–228).

In animal studies, Buquineran had a positive inotropic and vasodilator effect with minimal effects on heart rate. Studies in normal humans (229, 230) and in patients (103a, 227, 228, 231) all indicated that intravenous infusions of Buquineran (64–256 μg/kg/min) caused a positive inotropic effect in normal subjects and in both acute and chronic heart failure patients. However, many of these positive inotropic effects were abolished by pretreatment with a β-adrenergic blocking agent (227).

Thus, Buquineran is a phosphodiesterase inhibitor with a major effect on NE release that in turn increases the inotropic state of the heart.

Cilostamide

Cilostamide is a cyclic AMP phosphodiesterase inhibitor prepared by Kohri et al (232); its pharmacology was studied by Endoh et al (233).

Cilostamide had one-third the potency of 1-methyl-3-isobutylxanthine (IBMX) in inhibiting a crude amine cyclic AMP phosphodiesterase, but it was 10 times more potent than IBMX in enhancing the isoprenaline-induced increase in cardiac contractility and it potentiated the effects of isoprenaline on cardiac cyclic AMP production (233). Cilostamide increased sinus rate at lower concentrations than those that increased contractile force on isolated auricles, and a β-adrenergic blocker reduced the inotropic effects by about 50%. The results suggest that cilostamide releases NE and is a phosphodiesterase inhibitor with rather modest effects on cardiac contractility.

Phthalazinol (EG626)

Phthalazinol (see Table 3) is a phosphodiesterase inhibitor the cardiac effects of which were studied by Shigenobu et al (234). In comparison with theophylline, it produced greater effects on heart rate and contractile force and showed a separation of inotropic and chronotropic effects in the isolated auricle. All these effects were resistant to β blockade. Phthalazinol potentiated the effects of isoproterenol, which supports the concept that this drug is a phosphodiesterase inhibitor. At lower concentrations, phthalazinol had no effect on the atrial and ventricular action potentials. At high concentrations, the rising phase of the action potential was depressed and it prolonged the action potential. In depolarized muscle, phthalazinol produced the slow response, which was abolished by Mn^{2+}, verapamil, and low Ca^{2+} concentration. It is possible that these effects on inotropism and chronotropism are related to the increase in the slow current, which is induced by the increased concentration of intracellular cyclic AMP.

USV 2776

This compound is one of a series of dihydro- and tetrahydroisoquinolines and is a phosphodiesterase inhibitor, especially of the insoluble fraction obtained from frog and dog heart muscle. It has I_{50} of 4–6 μM on insoluble cyclic AMP and cyclic GMP phosphodiesterase, while papaverine (8–16 μM), theophylline (130–150 μM), and MIX (12–19 μM) were less effective. No data on the cardiac effects of this compound are available.

INHIBITORS OF Na^+K^+-ATPase

This group of substances includes a variety of different chemical entities, including the cardiac glycosides (235) (see Table 4).

A large number of semi-synthetic cardio-active glycosides have been prepared in the hope of improving the therapeutic ratio of the naturally occurring glycosides (4, 5). With few exceptions, the methods used for the determinations of therapeutic efficacy and toxicity ratios are frequently difficult to

Table 4 Substances that inhibit Na^+K^+-ATPase and have positive inotropic effects, excluding cardiac glycosides and related structures

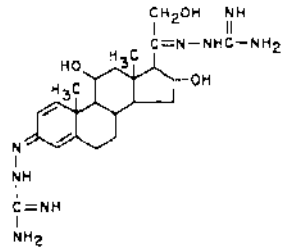
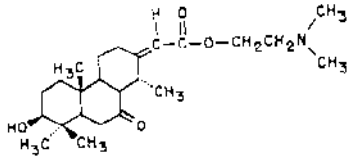
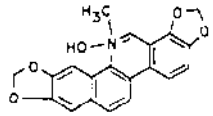
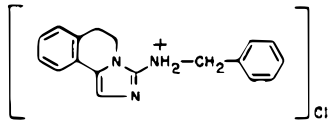
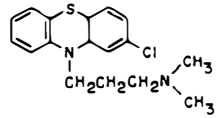
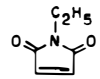
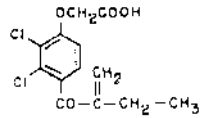
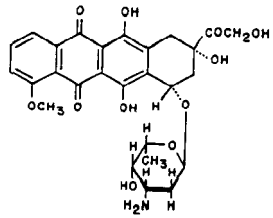
Name	Formula	References
Prednisone bisguanyl hydrazone (PBGH)		348–351
Erythrophleum-alkaloids cassaine		244, 245, 352–354
Sanguinarine		355, 356
Benzylamino-dihydro-dimethoxy-imidazo-isoquinoline (B11A)		259a, 357–359
Chlorpromazine and related substances		360–364
p-Chloromercuribenzoate; p-chloromercuri benzene sulfonic acid		248, 261, 365, 366
N-ethylmaleimide		248, 249, 367–369

Table 4 (*Continued*)

Name	Formula	References
Ethacrinic acid		370–373
Vanadate	Na_3VO_4	258, 259, 374
Rubidium	RbCl	235, 254–256b, 375
Thallous ion	$TiNO_3$	235, 255, 376–379
Doxorubicin		380–382

interpret. Methods for determining the minimal therapeutic, toxic, and lethal doses have been described by Farah & Maresh (236) in the isolated heart-lung preparation of the dog and by Walton et al (237) in intact dogs. The general methods have been reviewed by Bahrman & Greeff (238) and Greeff & Hafner (239). With the naturally occurring cardioactive compounds that are slowly inactivated, the constant infusion method of administering the glycosides produced results where the ratio of therapeutic-to-toxic doses was about the same for all compounds studied (236, 240–242). However, with rapidly inactivated and/or rapidly acting substances, such as dihydro cardio-active glycosides, the therapeutic-to-toxic ratio was increased (241). Similar findings have been reported for semi-synthetic cardio-active glycosides by Pastelin & Mendez (199), Mendez et al (242), and Bojorges et al (243). All these substances are rapidly destroyed and have a rapid onset of action, and thus both the therapeutic-to-lethal dose ratio and the toxic-to-lethal dose ratio are greater than the values obtained with ouabain. The rapid onset of action and destruction of these compounds could explain these findings.

Some nonglycosidic Na^+K^+-ATPase inhibitors have a positive inotropic effect in isolated cardiac tissue and only a few will be reviewed here. However,

the interested reader is referred to the comprehensive discussion by Akera et al (235).

Erythrophleum Alkaloids

The erythrophleum alkaloids (see Table 4) are diterpenoid acids esterified with β-methylamino ethanol or β-dimethylaminoethanol. The best known of these alkaloids are erythropheleine, cassaine, and cassaidine and all have cardiotonic properties similar to those observed with cardio-active glycosides (244). Krayer et al (245) have shown that erythrophleic acid per se has no positive inotropic effect, although the pertinent amino alcohols, including mono- and di-methylamino ethanol, had positive inotropic effects that were about 1/200 that of cassaine and in high doses produced cardiac irregularities. This suggests that the active moiety is the aminoalcohol and esterification increases the cardiac effects.

Cassaine and related alkaloids like the cardio-active glycosides block the uptake of K^+ in human red blood cells and inhibit Na^+K^+-activated ATPase in homogenates and partially purified enzyme preparations obtained from a variety of tissues and species (235).

Sulfhydryl Inhibitors

Older studies have shown that $HgCl_2$ and organic mercurial diuretics (see Table 4) are negative inotropic and produce severe cardiac irregularities and ventricular fibrillation. On the other hand, p-chloromercuribenzoate was relatively nontoxic to the heart and the end point was a cardiac standstill (246). The diuretic effects of both $HgCl_2$ and organic mercurial diuretics could be inhibited or reversed by p-chloromercuribenzoate (247a, 247b), thus indicating different mechanisms of action of p-chloromercuribenzoate on the heart and kidney. Other sulfhydryl reagents, such as N-ethylmaleimide, inhibit Na^+K^+-ATPase and have a positive inotropic effect in isolated cardiac tissue (235, Table 4), which can sometimes be reduced but not eliminated by reserpine or propranolol pretreatment (248).

However, in a number of instances, the inotropic effect of the sulfhydryl inhibitor does not correlate well with its capacity to block Na^+K^+-ATPase. Thus, Fricke (249) has observed a half-maximal effect on contractile force of guinea-pig papillary muscle at 9 μM concentration of N-methylmaleimide, while 50% inhibition of Na^+K^+-ATPase required 1 mM concentration. Furthermore, the mercurial diuretics and $HgCl_2$ are also powerful inhibitors of the Na^+K^+-ATPase (250, 251) but have predominantly negative inotropic effects on heart tissue (252, 253).

Other Na^+K^+-ATPase inhibitors have a positive inotropic effect, although the correlation between ATPase inhibition and inotropic effect is not always positive. Thus, *rubidium ion* (Rb^+), which can replace K^+ in Na^+K^+-ATPase,

will inhibit the fully activated ATPase in guinea-pig ventricular tissue and will produce a positive inotropic effect in guinea-pig auricular tissue (254–256a). However, Knight & Nosek (256b) have observed that Rb^+ produced a negative inotropic effect in guinea-pig ventricular tissue, which paralleled a transient shortening of the action potential duration. When active transport of Na^+ was stimulated by a burst of high rate of stimulation (257), Rb^+ produced a block of repolarization in guinea-pig ventricular tissue similar to that observed with cardiac glycosides. These results show that although Rb^+ has inhibitory properties on ATPase and the sodium pump, it does not necessarily follow that this will increase the force of contraction.

Vanadate

Vanadate (see Table 4) is a potent inhibitor of Na^+K^+-ATPase (258) and increases the force of contraction of isolated rat and rabbit auricular and ventricular tissue and ventricular tissue of the cat and guinea pig (235). However, in guinea pig and cat auricular tissue, Vanadate is a negative inotropic agent, although it inhibits the isolated Na^+K^+-ATPase of both these tissues (259a).

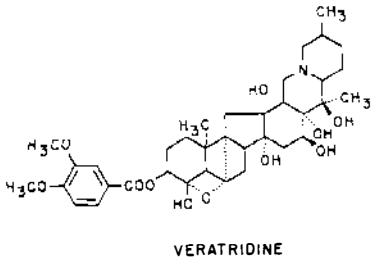
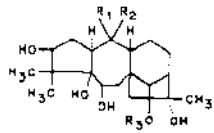
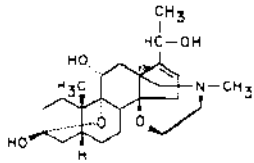
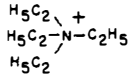
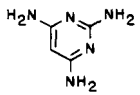
Erdman has shown that in rat ventricular muscle Vanadate actually increased Na^+K^+-ATPase activity and Grupp et al (259b) have reported that Vanadate increased cyclic AMP in the presence of propranolol in both ventricular and auricular guinea-pig muscle. Thus, the changes in cyclic AMP produced by Vanadate cannot explain the contractile effects of this ion. With Vanadate, there is a dissociation between inotropic action and inhibition of the Na^+K^+-ATPase; Vanadate inotropic effects may be related to an action on a calcium pool in the glyco-calyx part of the membrane (260) or possibly to prolongation of the sodium current, which manifests itself by a broadening of the action potential in responsive tissue.

Although not all Na^+K^+-ATPase inhibitors produce positive inotropic effects (261), it is rather striking that a number of these, such as p-chloromercuribenzoate, ethacrinic acid, and N-ethylmaleimide, have rather pronounced positive inotropic effects. It should be kept in mind that all these compounds may have effects other than the inhibition of the ATPase and that the inotropic effects could be negated by other effects of this highly reactive group of compounds.

Positive Inotropic Drugs that Prolong the Cardiac Action Potential

To the class of drugs that prolongs the cardiac action potential (see Table 5) belong the veratrum alkaloids, the grayanotoxins, the sea anemone polypeptides, the batrachotoxins, and scorpion poison, all of which prolong the action potential by an action on the sodium current. From studies on the squid

Table 5 Positive inotropic drugs that prolong the cardiac action potential

Name	Formula	References
Veratrum alkaloids Veratridine, Germitrine, Cevadin, Cevine	 VERATRIDINE	383–388
Andromedotoxins Grayanotoxins		262, 263, 389–391
Batrachotoxin		264–266, 392, 393
Anthopleurin-A Anthopleura *Xantho*grammica	Sequence of amino acids in Anthopleurin-A GLY-VAL-SER-CYS-LEU-CYS-ASP-SER-ASP-GLY-PRO-SER-VAL-ARG-GLY-ASN-THR-LEU-SER-GLY-THR-LEU-TRP-LEU-TYR-PRO-SER-GLY-CYS-PRO-SER-GLY-TRP-HIS-ASN-CYS-LYS-ALA-HIS-GLY-PRO-THR-ILE-GLY-TRP-CYS-CYS-LYS-GLN	271, 277, 283, 286, 394–396
ATXII Anemonia Sulcata	GLY-VAL-ILE*-PRO-CYS-LEU-CYS-ASP-SER-ASP-GLY-PRO-SER-VAL-ARG-GLY-ASN-THR-LEU-SER-GLY-ILE-ILE-TRP-LEU-ALA-GLY-CYS-PRO-SER-GLY-TRP-HIS-ASN-CYS-LYS-HIS-GLY-PRO-THR-ILE-GLY-TRP-CYS-CYS-LYS-GIN	45, 273, 275
Scorpion poison		397, 398
Tetraethylammonium ion		399–403
2,4,6,Triaminopyrimidine		267

axon, Purkinje fibers, and cardiac muscle tissue, it has been suggested that these toxins increase sodium influx by increasing the resting sodium permeability (262–265). However, Honerjäger & Reiter (266) suggest that the delay in repolarization produces a prolonged sodium influx that in turn increases Ca^{++} entry. The positive inotropic effects of triaminopyrimidine and tetraethyl ammonium are probably best explained by postulating reduction in potassium conductance by these agents, possibly due to a binding to a calcium site that regulates potassium conductance (267–270).

Anthopleurin-A (AP-A)

Anthopleurin-A (AP-A) (see Table 5) is a polypeptide containing 48 amino acids (molecular weight 5195) that was isolated by Norton et al (271) from the sea anemone *Anthopleura xanthogrammica;* its amino acid sequence was determined by Tanaka et al (272). A closely related single-chain polypeptide, ATX11, was isolated by Beress & Beress (273) from a sea anemone *Anemonia sulcata*. Both these polypeptides seem to have very similar pharmacological effects on cardiac muscle (274–276). Shibata et al (277) determined the effects of AP-A on isolated cardiac tissue and intact cats and dogs. Inotropic effects were observed in rat-, rabbit-, guinea-pig-, and cat-isolated auricular tissue; the toxin was about as effective as isoproterenol ($2–5 \times 10^{-9}$ M) in increasing contractility of the heart but did not increase heart rate significantly. In intact dogs and cats, AP-A (0.5 μg/kg) increased contractile force and dp/dt, decreased heart rate, and produced no change in blood pressure. When large doses (10 μg/kg) were given, cardiac arrhythmias appeared (277–279). In isolated cardiac tissue, the major effects of AP-A were an increased contraction or tension development and an increase in the total duration of contraction, which was mainly due to a prolongation of the rate of relaxation (275).

The effects of AP-A on cardiac contractility were not inhibited by reserpine pretreatment or by a β blocker and no effect on a cardiac Na^+K^+-ATPase preparation could be demonstrated (277). In a calcium-deficient medium AP-A was able to restore contraction, suggesting that external Ca^{++} ion is not required for the inotropic effect of AP-A. However, ryonodine (277) and dantroline (280) inhibited the effects of AP-A on contractile force of the heart. Ryonodine blocked the intracellular translocation of Ca^{++} in cardiac muscle (281) and dantroline reduced calcium release from the sarcoplasmic reticulum of skeletal muscle (282). These data suggest that AP-A action may involve the mobilization of intracellular calcium ion. Electrophysiological studies on heart muscle have shown that the main effect of AP-A is a prolongation of the action potential and an increase in the refractory period. Resting potential and rate of rise of the action potential were not affected; however, the plateau phase was prolonged and repolarization time was increased (275, 277, 283–286). Koda-

ma et al (285) and Beress et al (45) have shown that the anemone toxins prolonged the action potential and this change was greater at lower than at high rates of stimulation. Hashimoto et al (286) have applied voltage clamps to cardiac tissue and have shown that the prolongation of the action potential by AP-A is accompanied by a decreased net outward current. The slow inward current and the potassium outward current were not affected. The prolongation of the action potential by AP-A was reversed by lowering outside Na^+ concentration and by tetrodotoxin (275, 276, 286, 287). The electrophysiological data suggest that AP-A has a major effect on prolonging the sodium current. This would cause an increased Na^+ entry and, indirectly by activating the Na^+-Ca^{++} exchange mechanism, result in increased Ca^{++} concentration and contractile force. However, experiments with ryonodine and dantroline suggest that AP-A may also act by increased translocation of intracellular calcium.

No human data with AP-A have come to our attention. However, because it is a relatively large foreign polypeptide, the formation of antibodies to AP-A may limit its usefulness in therapy.

Miscellaneous Inotropic Agents

FORSKOLIN Forskolin (see Table 6) is a cardiotonic agent (288) isolated from the Indian herb *Coleus forskohlii* (288, 289). A closely related compound, coleonol, was isolated by Tandon et al (quoted in 290) from *Coleus forskohlii;* it also has inotropic and chronotropic effects on the heart. Forskolin is a diterpene (see Table 6) with an ester bond on Carbon 7. It should be pointed out that the erythrophleum alkaloid cassaine is also a diterpene ester where the alcohol is dimethylamino ethanol.

Lindner et al (288) described the effects of Forskolin on the isolated and in situ heart. This compound is a powerful cardiac stimulant in concentrations as low as 5×10^9 gm/ml. The time to peak tension and relaxation time were not changed by Forskolin. Microelectrode studies have shown that the action potential is shortened, especially with higher concentrations of Forskolin (5 μg/ml); however, the rate of rise of the 0-phase, the overshoot, and the plateau are not significantly changed. In higher concentrations, Forskolin produces spontaneous depolarization (288).

In intact anesthetized cats, Forskolin had positive inotropic and chronotropic effects and reduced blood pressure.

Forskolin does not inhibit either phosphodiesterase or Na^+K^+-ATPase but it depletes K^+ from the heart. In rat heart slices, Metzger & Lindner (291) observed that Forskolin induced a reduction of Na^+K^+-activated ATPase that accompanied the increase in cyclic AMP.

The mechanism of action of Forskolin was studied by Metzger & Lindner (292) and Holzmann et al (293), who observed that in intact cardiac tissue, as well as cardiac slices and membranes from rats, guinea pigs, and rabbits,

Table 6 Miscellaneous compounds

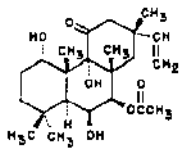
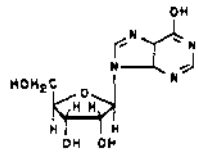
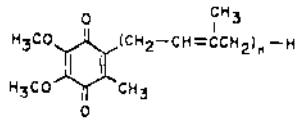
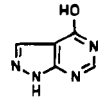
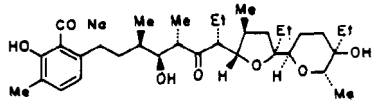
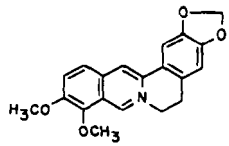
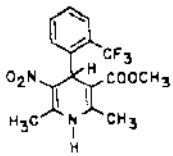
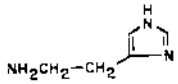
Name	Formula	References
Forskolin		288, 290, 292, 404
Inosine		405, 406
Coenzyme Q_{10} Ubiquinone (10)		299–303, 407
Glucagon	HIS-SER-GEN-GLY-THR-PHE-THR-SER-ASP-TYR-SER-LYS-TYR-LEU-ASP-SER-AVG-AVG-ALA-GLN-ASP-PHE-VAL-GLN-TYR-LEU-HET-ASN-THR	409a, 409b
Secretin	HIS-SER-ASP-GLY-THR-PHE-THR-SER-GLU-LEU-SEV-AVG-LEU-AVG-ASP-SER-ALA-AVG-LEU-GLU-AVG-LEU-LEU-GLU-GLY-LEU-VAL-NH_2	410–413
Vasoactive intestinal polypeptide	HIS-SER-ASP-ALA-VAL-PHE-THR-ASP-ASN-TYR-THR-ARG-LEU-ARG-LYS-GLN-MET-ALA-VAL-LYS-LYS-TYR-LEU-ASN-SER-ILE-LEU-ASN	413–415
Allopurinol		416
Ionophore antibiotics Lasalocid (X537A)		417–419
Berberine		420a–423
Aminoethanol	H_2N-CH_2-CH_2OH	245
Na Fluoride	Na	424–429

Table 6 (*Continued*)

Name	Formula	References
Na Fluoro-acetate	FCH_2COOH	426, 430–432
Cholera-toxin	Molecular weight 83,000	309, 433
Imidazole		435
Taurine	$HO_3S.\ CH_2CH_2\text{-}NH_2$	435–440
Frapadil		
BAYK 8644		441
Histamine		442–446

Forskolin increased the cardiac content of cyclic AMP and the activity of protein kinase.

These interesting observations with Forskolin on adenylate cyclase have been extended by Daly and his coworkers and Seamon and Seamon & Daly (290). Daly (294a) has recently reviewed the biochemical aspects of Forskolin action. The data available show that Forskolin increased cyclic AMP by an action on the catalytic unit of the adenylate-cyclase system. Recently, Brooker et al (294b) have observed that the effects of Forskolin on the adenylate-cyclase system of C6–2B rat astrocytoma cells is markedly inhibited by the protein synthesis inhibitors emetine or cycloheximide. These experiments suggest that a protein with a relatively short half-life is essential for the adenylate-cyclase system, which is stimulated by Forskolin. One can surmise that this protein is the site of action of Forskolin and that this protein relates to the activity of the catalytic unit of the adenylate cyclase.

COENZYME Q_{10} Coenzyme Q_{10} (CoQ_{10}) was isolated in 1959 by Crane et al (295) and is concentrated in mitochondria of various organs, including cardiac muscle. The biochemistry and pathophysiology of CoQ_{10} has been recently reviewed (296). The main points of this review are that a 75% depletion of cardiac CoQ_{10} leads to serious impairments of cardiac function and that the concentration of CoQ_{10} was markedly reduced in hearts obtained from heart

failure cases (297). Clinical studies, although uncontrolled, have claimed that CoQ_{10} administration causes improvement in patients suffering from congestive heart failure (298).

Recent experimental studies have shown that administration of CoQ_{10} protects the heart from the functional damage produced by ischemia hypoxia or metabolic inhibitors such as adriamycin or dinitrophenol (299–303). All these studies indicate that CoQ_{10} administration reduces the effects of hypoxia and anoxia on both the contractile force and on the slow calcium-dependent action potential observed in depolarized cardiac muscle (303).

The data on CoQ_{10} and cardiac function is quite limited and the usefulness of this compound in the treatment of heart failure will require controlled double-blind clinical evaluation before any judgment can be passed. However, the importance of CoQ_{10} as a redox component between NADH and cytochrome b-c_1 complex makes this coenzyme an essential component for energy production in cardiac muscle and its deficiency will have serious consequences for heart function (304).

CYCLIC NUCLEOTIDE ANALOGS Earlier studies have shown that exogenously applied cAMP or cyclic AMP analogs (see Table 6) mimic the response to β-adrenergic agonists (159, 305–308). These substances produce a positive inotropic effect, decrease the duration of contraction, suppress potassium contractures, and increase calcium uptake in heart muscle, but are several magnitudes less potent than the adrenergic agonists. These effects are observed after reserpine and β-adrenoreceptor blockade. The findings of Li & Sperelakis (309) that intracellular injection of cyclic AMP increases the slow action potential of cardiac cells depolarized by 22 mM K^+-Tyrode solution is further evidence that cyclic AMP mimics the effects of β-adrenergic agonists.

Since cyclic AMP is rapidly destroyed, more stable analogs have been prepared that have inotropic effects in isolated cardiac preparations (310, 311). It should be kept in mind that these cyclic AMP analogs can act either as activators of protein kinase or as inhibitors of phosphodiesterase, thus mimicking effects of β-adrenergic agonists of phosphodiesterase inhibitors.

CALCIUM IONOPHORES The ionophores, "ion bearers" (see Table 6), are natural or synthetic products of a molecular weight varying between 200 and 2000. They were discovered serendipitously by Pressman and his colleagues in 1964 through their effect of stimulating energy-linked transport in the mitochondria (312). The ionophores form lipid-soluble complexes with polar cations, such as the monovalent cations Na^+, K^+, Rb^+, Li^+, and Cs^+; the divalent cations Ca^{2+}, Ba^{2+}, Mg^{2+}, Mn^{2+}, and Sr^{2+}; and the biogenic amines epinephrine, norepinephrine, dopamine, and serotonin (313). Most ionophores have some selective affinity and complexing capacity (314).

When ionophores are added to biological membranes, they form lipid-soluble cation complexes capable of rapid diffusion across the membrane. The dynamic reversibility of the complex at the membrane interfaces enables the ionophore to behave as a mobile cation carrier within biological membrane (314).

In rabbit or guinea-pig ventricular strips, the carboxylic calcium ionophore X-537A caused increases in twitch tension and contracture. However, the muscle developed tachyphylaxis to the drug after the first treatment. In addition, no inotropic response was observed after pretreatment of the preparation with propranolol on depletion of cardiac catecholamines with reserpine (315). The catecholamine and Ca^{2+} mobilization effect of the ionophores could be differentiated in cardiac strips treated with propranolol where the inotropic response to small doses of X-537A disappeared while the increase in tension and contracture could still be demonstrated (315).

Studies in anesthetized dogs (316, 317) showed that the intravenous administration of X-537A caused an increase in cardiac contractile force, slight increases in systolic and diastolic blood pressure, and no change in heart rate. The calculated total peripheral resistance was decreased. The translocation of Ca^{2+} and catecholamines was considered the mechanisms for the positive inotropic activity of X-537A.

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