Nicorandil, although structurally a nitrate, differs from classic nitrates in several respects. It preferentially dilates resistive vessels. Its effect on venous return in dogs is not unanimously a decrease but rather an increase. In high doses or concentrations it suppresses myocardial contraction and ventricular automaticity, nearly sparing sinoatrial nodal automaticity and atrioventricular nodal conduction. It shortens the effective refractory period of myocardium. These cardiac effects of nicorandil have been explained by its mechanism of action as a potassium (K) channel activator. However, what part of the vascular effects of nicorandil this mechanism is responsible for has not been determined. BRL 34915 and pinacidil, nonnitrate vasodilators with a K-channel activator action, have essentially the same cardiovascular profile as nicorandil in isolated, blood-perfused canine heart preparations. In anesthetized, open-chest dogs the 2 K-channel activators decreased systemic blood pressure and increased venous return and cardiac output without elevating heart rate, unless the cardiodepressant effect emerged. The increase in venous return or cardiac output survived elimination of baroceptor functions. These results taken together with previous results on nicorandil suggest the following: (1) The property of nicorandil as a resistive vessel dilator highly selective for vasculature originates in its mechanism of action as a K-channel activator. The nonunanimous effect of nicorandil on venous return is a result of the opposing actions as a capacitive (action as a nitrate) and a resistive vessel dilator. Nicorandil, with its hybrid nature, is advantageous over specific K-channel activators and classic nitrates in therapeutic implications.

(Am J Cardiol 1989;63:18J–24J)

Nicorandil is a nitrate in chemical structure (Fig. 1). However, basic pharmacologic experiments of nicorandil in the past decade have revealed that the drug has at least a dual mechanism of action; one is related to its chemical structure as a nitrate and the other is unrelated.1 An increase in intracellular cyclic guanosine monophosphate (GMP) in vascular2,3 and cardiac4 tissues produced by nicorandil appears to be derived from the mechanism of action as a nitrate. The mechanism of action most uncharacteristic of classic nitrates such as nitroglycerin and isosorbide dinitrate but characteristic of nicorandil is an increase in membrane potassium (K) conductance in cardiac muscle1,5–8 and vascular smooth muscle.9–12

The cardiodepressant actions of nicorandil first found in isolated, blood-perfused canine heart preparations, although evident in only high doses or concentrations, were exerted preferentially on myocardial contraction13 and ventricular automaticity,5 nearly sparing sinoatrial (SA) nodal automaticity and atrioventricular (AV) nodal conduction.13 Shortening of the effective refractory period of myocardium was also characteristically seen with nicorandil.5 However, these effects are entirely uncharacteristic of classic nitrates. The cardiodepressant actions of nicorandil are also different from those of calcium (Ca) channel blockers, which depress not only myocardial contraction but also SA nodal automaticity and AV nodal conduction; however, it does not affect the automaticity of Purkinje fibers.14 These cardiac effects of nicorandil are easily explained in terms of an increase in K conductance in the cardiac cell membrane.1 An increase in intracellular cyclic GMP produced by any means appears not to be related to either negative or positive inotropy in cardiac muscle (Yanagisawa et al, unpublished observations). Thus, with regard to cardiac effects of nicorandil, an increase in membrane K conductance or the mechanism of action as a K-channel activator appears to be solely responsible.

Unlike cardiac muscle, in vascular smooth muscle both the increase in intracellular cyclic GMP15,16 and hyperpolarization resulting from an increase in membrane K conductance9,17 lead to relaxation. Therefore, the questions arise as to what extent the action as a nitrate or as a K-channel activator is responsible for the vascular effect of nicorandil, and under what conditions either of the 2 mechanisms of action prevails. These questions were addressed in a previous overview on nicorandil.1 In vascular smooth muscle cells in which the membrane potential is positive to the K equilibrium potential that is thought to be located at about −70 mV, nicorandil hyper-
polarizes the membrane by increasing the membrane K conductance. When the membrane is hyperpolarized, voltage-dependent Ca channels are less likely to open. Consequently, the Ca influx through these Ca channels ceases and eventually vascular smooth muscle relaxes. Nevertheless, in this case an involvement of increased intracellular cyclic GMP as the relaxant effect of nicorandil is still possible. Conversely, in vascular smooth muscle cells in which the membrane potential is close to the K equilibrium potential, the relaxant action of nicorandil is independent of the mechanism of action as a K-channel activator and involves at least an increase in intracellular cyclic GMP. However, current information on the electromechanical effects of nicorandil on vascular smooth muscle cells, which display a great diversity depending on animal species and organs, is so limited that it is still difficult to explain all of its vascular effects in terms of its cellular effects.

One of the vascular effects of nicorandil that is uncharacteristic of classic nitrates revealed so far is an increase in coronary blood flow,\(^1,13,18,19\) or a decrease in resistance in the coronary arterial bed\(^20\) occurring monophasically and sustainedly in anesthetized or conscious dogs when nicorandil is given intravenously (i.v.). This effect suggests that nicorandil is a resistive vessel dilator because such an effect is characteristic of resistive vessel dilators. The question is whether such an effect of nicorandil is explainable in terms of its mechanism of action as a K-channel activator. Unequivocal results on venous return or cardiac output obtained with nicorandil in dogs (i.e., its effect ranges from an increase\(^13,18,20\) to a decrease\(^21\) through nearly no change\(^19\) contrast with unanimous results obtained with classic nitrates (i.e., they definitely decrease venous return in the same species).\(^22,23\) In the previous overview on nicorandil\(^1\), the question as to why unequivocal results had been obtained with nicorandil on venous return was answered as follows: A decrease in venous return produced by nicorandil, which is capable of increasing venous capacitance as a nitrate but for some reasons is weaker than classic nitrate in this respect, is variously modified by sympathetic reflex that increases venous return by decreasing venous capacitance, depending on experimental conditions. However, no answer has been given to the question of why nicorandil is weaker than classic nitrates in decreasing venous return. Resistive vessel dilators such as Ca channel blockers increase venous return unless their cardiodepressant effect is pronounced.\(^22,23\) Thus, the weaker action of nicorandil may be a result of its action as a nitrate being offset by an action as a resistive vessel dilator. These 2 questions will be answered with studies on the effects of nicorandil compared with those of a specific K-channel activator. BRL 34915, developed as an antihypertensive agent,\(^24\) has been shown to have K-channel activation in vascular smooth muscle as its relaxant mechanism\(^25\) and to be more specific than nicorandil in this respect.\(^26\) Unfortunately, however, information on the cardiohemodynamic effects of this K-channel activator was very limited when the overview on nicorandil\(^1\) was being prepared. Recent reports on the cardiovascular effects of BRL 34915 and pinacidil (another antihypertensive agent\(^27\)) with the action as a K-channel activator\(^28,29\) have been reported. Thus, this article discusses what part of the cardiovascular effects of nicorandil is ascribable to the action as a K-channel activator and what part as a nitrate, based on these data.

**CARDIAC EFFECTS OF NICORANDIL ARE DUE ENTIRELY TO ACTION AS A K-CHANNEL ACTIVATOR**

As previously discussed,\(^1\) the cardiac effects of nicorandil are explainable in terms of the mechanism of action as a K-channel activator. This hypothesis has been confirmed by experiments with BRL 34915.\(^30\) In isolated, blood-perfused canine heart preparations, BRL 34915 had essentially the same cardiac profile as nicorandil. When BRL 34915 was administered in higher doses than those producing a sizable increase in coronary blood flow, it produced a decrease in the force of contraction of the papillary muscle; this contraction was nearly abolished at its maximal effect (Fig. 2). In some preparations, ventricular fibrillation occurred during a large decrease in the force of contraction of the papillary muscle and subsided spontaneously (Fig. 2). In similarly high doses, BRL 34915 reduced the rate of those spontaneous contractions of the unpaced papillary muscle that are thought to reflect the automaticity of Purkinje fibers in the ventricular septum to which the papillary muscle is attached. In contrast to such large suppressant effects on the force of contraction of ventricular muscle and the automaticity of Purkinje fibers, BRL 34915, even in large doses, suppressed SA nodal automaticity and AV nodal conduction.
A SYMPOSIUM: FOCUS ON NICORANDIL

FIGURE 2. Effects of BRL 34915 on blood flow through the anterior septal artery (top) and the force of contraction of the papillary muscle (bottom) paced at a fixed rate of 120 stimuli per minute of an isolated, blood-perfused papillary muscle preparation of the dog. BRL 34915 was injected in a single bolus infusion into the anterior septal artery. Note that at 100 μg of BRL 34915, ventricular fibrillation (VF) ensued from the profound negative inotropic effect and subsided spontaneously. (Reproduced with permission from J Cardiovasc Pharmacol.26)

to only a smaller extent.30 Because BRL 34915 has been shown to have no actions other than that as a K-channel activator,26 these cardiac effects should be considered characteristic of specific K-channel activators. The close resemblance of the cardiac profile between BRL 34915 and nicorandil indicates that the cardiac action of nicorandil is due entirely to its action as a K-channel activator. Essentially similar cardiac effects have been observed with pinacidil.31 Differences among the 3 K-channel activators lie in their potencies; BRL 34915 was about 4 times as potent as pinacidil, which in turn was about 20 times as potent as nicorandil on a weight-to-weight basis.10

NICORANDIL OWES HIGH VASCULAR SELECTIVITY TO ACTION AS A K-CHANNEL ACTIVATOR

In isolated, blood-perfused canine heart preparations nicorandil increased coronary blood flow in doses that exerted virtually no effect on cardiac variables such as the force of contraction,13 sinus rate,13 AV nodal conduction time13 and ventricular rate.5 However, in the early stages...

FIGURE 3. Selectivity spectra for coronary blood flow vs cardiac variables of nicorandil, BRL 34915 and pinacidil delineated by use of isolated, blood-perfused canine heart (sinoatrial [SA] node, atrioventricular [AV] node and papillary muscle) preparations. The selectivity for coronary blood flow compared with cardiac variables is defined as the ratio of the potency in affecting a cardiac variable to the coronary vasodilator potency. (Data for nicorandil are adapted from Clin Exp Pharmacol Physiol.13 The selectivity spectra of BRL 34915 and pinacidil are reproduced with permission from Jpn J Pharmacol.31)
The investigation of nicorandil could not determine whether its high selectivity for coronary vasculature vs myocardium was a result of its actions in up to medium dosages only as a nitrate or the result of the same mechanism responsible for cardiac effect acting on coronary vasculature with low doses to dilate it. In other words, at that time it was still unknown whether an increase in K conductance with nicorandil was more effective in vascular smooth muscle to relax it than in cardiac muscle to depress it. This problem has now been solved by experiments with BRL 34915. Similar to nicorandil, BRL 34915 increased coronary blood flow in doses far lower than those that exerted cardiac effects. Figure 2 shows the predominant coronary vasodilator effect of BRL 34915 compared with the depressant effect on the force of contraction in an isolated, blood-perfused papillary muscle preparation of the dog. Essentially the same feature has been observed with pinacidil. Figure 3 shows the cardiovascular profiles of nicorandil, pinacidil and BRL 34915 delineated by use of isolated, blood-perfused canine heart preparations. The 3 agents had essentially the same cardiovascular profile and were highly selective for coronary vasculature compared with myocardium. Thus, the high selectivity of nicorandil for coronary vasculature is not necessarily due to its being a nitrate. K-channel activators are highly selective for coronary vasculature vs myocardium.

It has been established that classic nitrates are more selective for large conductive coronary vessels than small resistive vessels in the coronary arterial bed. In other words, although intracoronary classic nitrates increase coronary blood flow, a decrease in resistance is more prominent in large conductive coronary arteries than in small resistive vessels in the coronary arterial bed. In contrast to the preferential dilator effect of classic nitrates on large conductive coronary arteries, nicorandil preferentially dilates small resistive vessels in the normally perfused coronary arterial bed of the canine heart. A decrease in resistance in large conductive coronary arteries was demonstrable only under conditions in which the coronary perfusion pressure was reduced to nearly half the normal value. Therefore, nicorandil should be characterized as a resistive vessel dilator, although it retains the property as a nitrate in dilating large conductive coronary arteries. The property of nicorandil as a resistive vessel dilator appears to originate in its mechanism of action as a K-channel activator.

In summary, nicorandil shares the properties for dilating resistive vessels in the coronary arterial bed and for being highly selective in coronary vasculature vs myocardium.
A SYMPOSIUM: FOCUS ON NICORANDIL

The property of nicorandil as a highly selective coronary vasodilator is that of a K-channel activator.

**EFFECT OF NICORANDIL ON VENOUS RETURN AS A SUM OF EFFECTS AS A NITRATE AND A K-CHANNEL ACTIVATOR**

This section discusses whether unequivocal results obtained with the effect of nicorandil on venous return (even in the single species, dogs), or its definitely weaker action than that of classic nitrates in reducing venous return, are explainable in terms of its dual action on blood vessels as (1) a resistive vessel dilator (or a K-channel activator), and (2) a capacitive vessel dilator (or a nitrate). To solve this problem, experiments were performed to see how the specific K-channel activator, BRL 34915, affects venous return using closed-loop preparations of pentobarbital-anesthetized dogs.34 The preparations were briefly: The chest was opened by a midsternal incision and the dog was maintained with positive-pressure respiration by use of a canine respirator. Noncannulating-type flow probes were instrumented at the pulmonary artery, and the superior and the inferior vena cava. Pulmonary artery flow was taken to represent cardiac output, and superior and inferior venae cavae flows to represent venous return. In addition to these hemodynamic variables, systemic arterial blood pressure, right atrial pressure, heart rate, AV conduction time, and the first derivative of left ventricular pressure (LV dP/dt) were measured. Figure 4 shows a typical experiment with BRL 34915 and data are summarized in Table I. BRL 34915, 3 to 30 µg/kg i.v., produced dose-dependent increases in superior and inferior venae cavae and pulmonary artery flows concomitantly with a decrease in systemic blood pressure. When 100 µg/kg, i.v. BRL 34915 was administered, inferior vena cava and pulmonary artery flows were definitely reduced for about 1.5 minutes, but after this brief period superior and inferior venae cavae and pulmonary artery flows increased. Initial transient decreases in these flows appear to be due to the depression of the myocardium, as reflected in increases in right atrial pressure and AV conduction time, and in a decrease in LV dP/dtmax. Similar phenomena have been seen with Ca channel blockers like verapamil.22,35 Because the increases in venous return and cardiac output produced by BRL 34915 may have been induced by reflex venoconstriction after hypotension, further investigation was carried out on how the cardiohemodynamic effects of BRL 34915 are modified by elimination of baroreceptor reflex. Baroreceptor reflex was eliminated by bilateral denervation of the carotid sinus and vagotomy. Under these conditions increases in pulmonary artery, inferior and superior venae cavae and pulmonary artery flows increased. Initial transient decreases in these flows appear to be due to the depression of the myocardium, as reflected in increases in right atrial pressure and AV conduction time, and in a decrease in LV dP/dtmax. Similar phenomena have been seen with Ca channel blockers like verapamil.22,35
with intact baroreceptors. Essentially similar results have been obtained with pinacidil. Thus, it is highly likely that K-channel activators as resistive vessel dilators increase venous return, and consequently cardiac output.

Because of the results obtained with the specific K-channel activators, unequivocal results obtained with nicorandil on venous return or cardiac output, or its weaker effect in reducing venous return, would have resulted from its dual action on venous return: (1) a decrease produced by an action as a nitrate, and (2) an increase produced by an action as a K-channel activator. Depending on which of the 2 actions is predominant, the effect on venous return may vary. When the 2 actions are balanced, nicorandil may fail to affect venous return or cardiac output.

ADVANTAGES OF NICORANDIL OVER CLASSIC NITRATES AND SPECIFIC K-CHANNEL ACTIVATORS

The antianginal efficacy of classic nitrates is thought to be mainly based on their 2 actions: (1) to dilate large conductive coronary arteries so that distribution of coronary blood flow to ischemic areas is favored; and (2) to reduce preload on the heart by decreasing venous return. The action of relieving coronary vasospasm occurring preferentially in large coronary arteries is also thought to be important. As previously described, in animal experiments the dilator action of nicorandil on large conductive coronary arteries was demonstrated under underperfused conditions. However, on angiography, nicorandil (4 mg injected into the right atrium over a period of about 2 minutes) dilated large coronary arteries in patients with coronary artery disease both with and without coronary spasm, although the extent of the coronary dilatation was less than that seen 3 minutes after sublingual administration of 1 tablet (0.3 mg) of nitroglycerin. In this case, nicorandil appears to have dilated large coronary arteries by its action as a nitrate. However, it is still premature to conclude that specific K-channel activators are ineffective in dilating large coronary arteries, because no angiographic data are available on their efficacy in large coronary arteries. If specific K-channel activators have no pronounced effect on large coronary arteries, nicorandil is superior to them as an antianginal vasodilator.

Although preload reduction produced by classic nitrates is thought to play a central role in relieving anginal attacks, pronounced preload reduction is by no means favorable for patients with coronary artery disease because it leads to fainting. In a clinical study comparing
the effects of nicorandil and nitroglycerin in patients with ischemic heart disease, nicorandil (4 mg injected into the right atrium) produced a smaller decrease (about 20%) in LV end-diastolic pressure than nitroglycerin (0.3 mg sublingually) (about 60%, p <0.01), although both drugs were almost equally effective in reducing mean systemic arterial blood pressure (less than 10%). Furthermore, despite a decrease in preload, cardiac index increased with nicorandil vs a decrease with nitroglycerin. Thus, nicorandil is less likely to produce fainting than classic nitroglycerin. No fainting has been reported in about 12,560 patients with coronary artery disease treated with nicorandil (personal communication, Chugai Pharmaceutical Co., Ltd.).

In healthy volunteers, nicorandil has been shown to be more effective in reducing afterload than in reducing preload compared withisosorbide dinitrate. This afterload reduction is thought to be due to its action as a resistive vessel dilator. The afterload-reducing action of nicorandil would compensate for the less pronounced action to reduce preload in relieving anginal attacks.

The increased perfusion of ischemic areas is thought to be one of the important mechanisms in the antiangiogenic efficacy of Ca channel blockers. Because nicorandil increases coronary blood flow as do Ca channel blockers, it could be effective in increasing perfusion of ischemic areas in addition to improving distribution of coronary blood flow to ischemic areas operating in a manner similar to classic nitrates.

Finally, in nicorandil, in having a dual mechanism of action, is superior to classic nitrates and specific K channel activators as an antiangiural drug. Such properties of nicorandil also fulfill the requirements for vasodilators in the treatment of congestive heart failure.

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