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Cardiovascular Effects of NT-1, a New Patch Form of Nitroglycerin, Alone and in Combination with Nifedipine in Conscious Dogs

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Abstract

The cardiovascular effects of NT-1, a new patch form of nitroglycerin, alone and in combination with nifedipine in conscious dogs were examined.

NT-1 (2·5 mg kg^{-1} nitroglycerin) decreased systolic blood pressure by 10–15%, while diastolic blood pressure and heart rate were not affected. Coronary blood flow and calculated rate-pressure product were decreased. These parameter changes occurred at 30 min after NT-1 application and remained constant for 8 h until NT-1 was removed. After administration of NT-1 in combination with nifedipine, systolic blood pressure was significantly decreased to a greater extent, and heart rate and coronary blood flow showed a tendency to increase compared with nifedipine alone. Rate-pressure product was not changed compared with that obtained on administration of nifedipine alone.

These results suggest that NT-1 may be applicable as a transdermal sustained release medication, and show that in combination with nifedipine, NT-1 can induce a large increase in coronary blood flow without further increasing rate-pressure product.

Nitroglycerin has been used for over one hundred years for the treatment of anginal syndromes associated with coronary artery disease and angina pectoris, and at present is still the most reliable drug for preventing or abolishing anginal attack. Nitroglycerin ameliorates myocardial ischaemia by reducing preload and increasing coronary blood flow to ischaemic areas by inducing relaxation of conductance vessels. Nitroglycerin also shows weak reducing effects in afterload (Ahlner et al 1994).

More recently, various types of long-acting nitrates such as slow-release tablets, tape, ointment, and intravenous infusions, have been developed for increased clinical usefulness and are used widely. NT-1 (nitroglycerin tape, Herzer) used in this study was developed by Taiho Pharmaceutical Co. as a new type of transdermal sustained action medication. Unlike other patch-type nitroglycerins, NT-1 releases nitroglycerin which reaches maximum serum concentration one to two hours after application, followed by a gradual decrease in serum concentration (Idzu et al 1986). The symptomatic benefits of NT-1 in angina pectoris or acute heart failure have been demonstrated in dogs (Furuta et al 1993) and patients (Hirosawa et al 1986; Noda et al 1987).

The calcium antagonist nifedipine has been used clinically for more than a decade. Because of its strong peripheral and coronary artery-dilating action, nifedipine reduces left ventricular afterload and increases coronary sinus blood flow, although myocardial oxygen consumption does not appear to be significantly decreased (Schanzenbächer et al 1983).

Nitroglycerin and nifedipine are frequently used together in patients with coronary artery disease. In this study, we examined the cardiovascular action of NT-1 alone and in combination with nifedipine in conscious dogs, because the cardiovascular effects of vasodilating drugs are modified by systemic regulatory mechanisms in-vivo.

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Materials and Methods

Animals

All experiments were conducted in accordance with guidelines established by the Taiho Review Committee of Animal Experimentation.

Beagle dogs, 8·1 to 11·0 kg were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.v.) and ventilated artificially using an artificial respirator (SN-480-3, Shinano Co., Tokyo, Japan) with room air through an endotracheal cannula. Left thoracotomy was performed at the fifth intercostal space, and an ultrasonic flow probe (HDS25-20SA, 2·5 mm, Crystal Biotech, Hopkinton, MA, USA) was placed around the left circumflex coronary artery. For the measurement of blood pressure, an arterial catheter (PE-90, Clay-Adams, Parsippany, NJ, USA) was introduced into the abdominal aorta through the femoral artery. The tip of the cannula segment was led subcutaneously through an inguinal incision to the back of the neck. The cannula was filled with heparin solution and stopped with a steel wire plug. These procedures were performed under sterile conditions and antibiotics were administered intramuscularly to prevent infection.

The dogs were placed in a soundproof room for a recovery period of 5–10 days following the operation. Blood pressure was registered directly and continuously through the cannula and a pressure transducer (TP-300T, Nihon Kohden, Tokyo, Japan) connected to the pressure

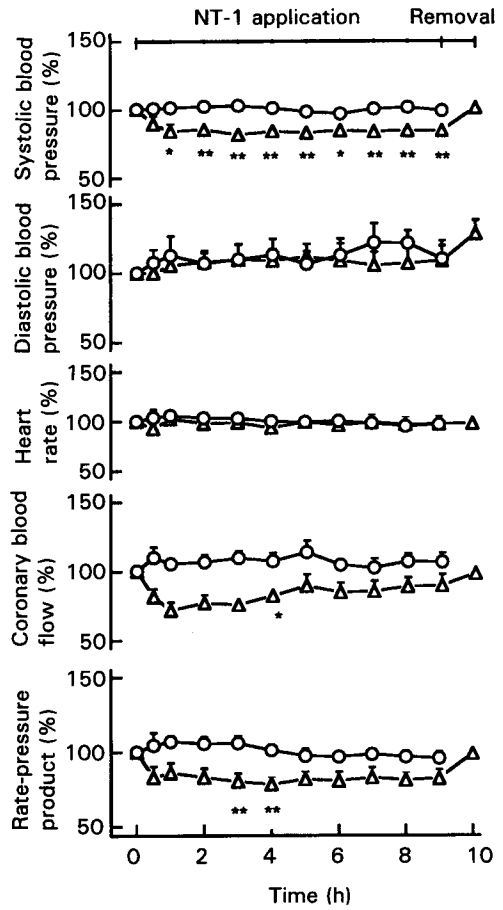

FIG. 1. Effects of NT-1 application (2·5 mg kg^{-1} nitroglycerin) to an area of shaven chest skin (Δ; O control) on percent control systolic blood pressure, diastolic blood pressure, heart rate, coronary blood flow and rate-pressure product in conscious dogs (mean ± s.e.m., n = 5). *$P < 0.05$ and **$P < 0.01$, significantly different from control. Control values are given in the Results section.

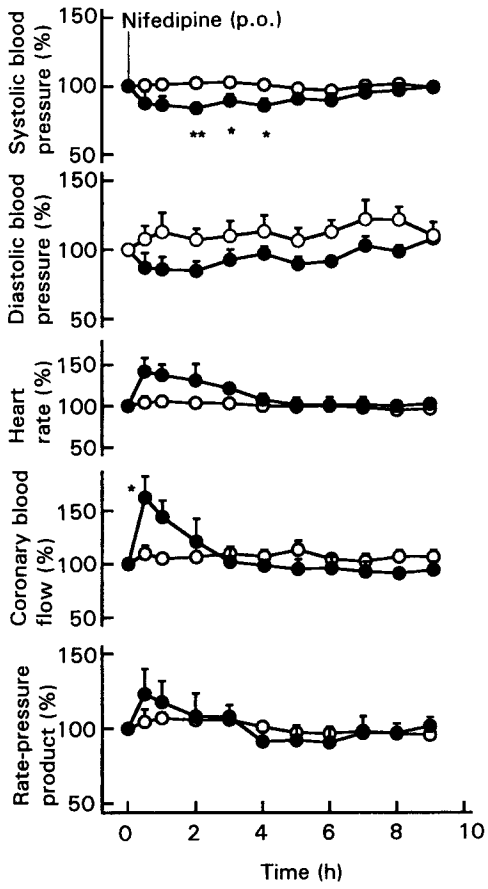

FIG. 2. Effects of oral administration of nifedipine (3 mg kg^{-1}) (●; O control) on percent control systolic blood pressure, diastolic blood pressure, heart rate, coronary blood flow and rate-pressure product in conscious dogs (mean ± s.e.m., n = 5). *$P < 0.05$ and **$P < 0.01$, significantly different from control. Control values are given in the Results section.

amplifier (AP-601G, Nihon Kohden) with the animals conscious and unrestrained. Heart rate was recorded with a cardiotachometer (AT-601G, Nihon Kohden) triggered by arterial pulse waves. Coronary blood flow was measured with a pulsed doppler flowmeter (VF-1, Crystal Biotech). Baseline values were recorded for 1 h and then the drugs were administered. The calculated rate-pressure product was presented as a product of systolic blood pressure and heart rate.

Drugs

Nitroglycerin tape (NT-1, 5 mg nitroglycerin per 5 × 10 cm^2) and placebo (base) tape were obtained from Taiho Pharmaceutical Co. (Tokyo, Japan) and applied at a dose of 2·5 mg kg^{-1} to an area of shaven chest skin. Nifedipine was purchased from a commercial source (Adalart capsule manufactured by Bayer Co., Osaka, Japan) and packed 3 mg kg^{-1} in gelatin capsules for oral administration under a yellow fluorescent lamp. In the control group, placebo tape was applied and blank capsule was administered orally simultaneously. The NT-1-treated group received blank capsules, and placebo tape was applied to the nifedipine-treated group.

Statistics

Data are expressed as means ± s.e.m. Multiple group comparisons were performed by one-way analysis of variance followed by Duncan's test. A P value <0·05 was considered statistically significant.

Results

Fig. 1 shows the effects of NT-1 on blood pressure, heart rate, coronary blood flow and rate-pressure product. The values of systolic blood pressure, diastolic blood pressure, heart rate, coronary blood flow, and rate-pressure product before drug administration were 158 ± 13 mmHg, 61 ± 6 mmHg, 102 ± 6 beats min^{-1}, 24 ± 4 mL min^{-1} and 16149 ± 1937 mmHg beats min^{-1}, respectively, for the control group. Systolic blood pressure was decreased by 10–15% by NT-1 application; diastolic blood pressure and heart rate were not affected. Calculated mean blood pressure was decreased by 5–8%. Coronary blood flow and rate-pressure product were decreased. These parameter changes occurred at 30 min after NT-1 application and remained constant for 8 h, recovering quickly after removal of NT-1.

Fig. 2 shows the effects of nifedipine on blood pressure, heart rate, coronary blood flow and rate-pressure product.

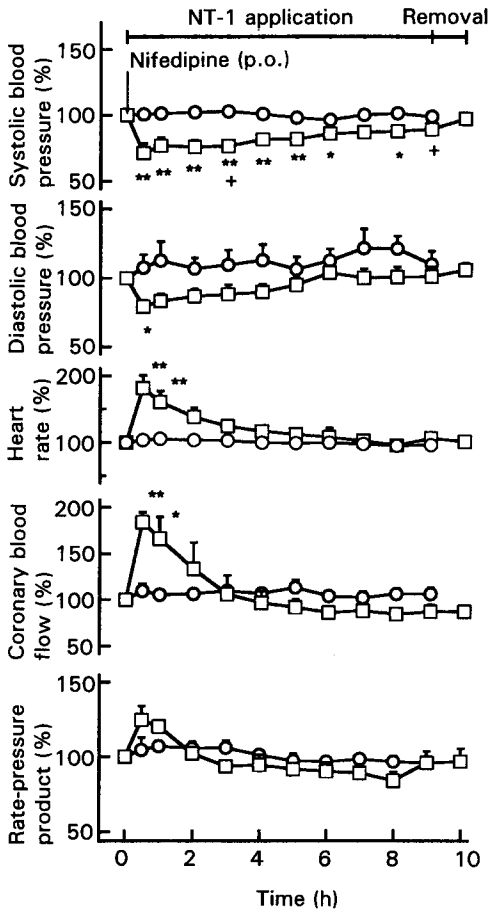

FIG. 3. Combined effects of NT-1 application (2·5 mg kg^{-1} nitroglycerin) to an area of shaven chest skin and oral administration of nifedipine (3 mg kg^{-1}) (□; ○ control) on percent control systolic blood pressure, diastolic blood pressure, heart rate, coronary blood flow and rate-pressure product in conscious dogs (mean ± s.e.m., n = 5). *$P < 0.05$ and **$P < 0.01$, significantly different from control. +$P < 0.05$, significantly different from nifedipine-treated group. Control values are given in the Results section.

Systolic blood pressure was decreased by nifedipine administration, and although diastolic blood pressure showed a decrease, this was not significant. Coronary blood flow was increased markedly; rate-pressure product showed a tendency to increase. These parameter changes reached a maximum at 30 min after oral nifedipine administration and recovered to baseline values within 4–6 h.

Fig. 3 shows the effects of combined administration of NT-1 and nifedipine. Systolic blood pressure was significantly decreased to a greater extent, and heart rate and coronary blood flow showed a greater tendency to increase compared with nifedipine alone. Rate-pressure product, in contrast, was not changed compared with that observed with nifedipine alone.

Discussion

We have demonstrated that NT-1 lowered blood pressure and decreased coronary blood flow and calculated rate-pressure product in conscious dogs. In combination, NT-1 and nifedipine induced a greater decrease in systolic blood pressure, and heart rate and coronary blood flow showed a tendency to increase greater than with nifedipine alone, while rate-pressure product was not changed compared with those changes with nifedipine alone.

NT-1 quickly lowered systolic blood pressure and decreased coronary blood flow after application, and these new levels then remained constant. The changed parameters quickly recovered after removal of NT-1. These results indicate that NT-1 may be applicable as a transdermal nitroglycerin delivery system. Mean blood pressure decreased by 5–8% after NT-1 application. An increase in the dose of nitroglycerin to decrease mean blood pressure by more than 10% might offset its potential for myocardial salvage in conscious dogs (Jugdutt 1983). Reflex tachycardia was not observed although systolic blood pressure was significantly lowered following administration of NT-1. The sympathetic nervous system is activated because of the large fall in blood pressure induced by relatively large doses of nitrate, whereas NT-1 releases nitroglycerin more slowly than sublingual or bolus intravenous administration (Idzu et al 1986). Coronary blood flow and rate-pressure product were decreased after NT-1 application. Bolus intravenous administration of nitroglycerin dilates the large coronary artery and increases coronary blood flow in anaesthetized or conscious dogs (Adachi et al 1987). With continuous injection of nitroglycerin, a biphasic response to nitrates in coronary flow was observed; a short-lived, pronounced increase in flow was followed by a longer-lasting decrease as a consequence of an increase in total coronary resistance (Rees et al 1966), and this was associated with a prolonged reduction of oxygen consumption. Similar observations have also been made in patients (Cowan et al 1969). Thus, decreased coronary blood flow after NT-1 application is a result of reduced afterload leading to a reduction in myocardial oxygen demand.

Nifedipine decreased systolic blood pressure and increased coronary blood flow, while heart rate showed a tendency to increase. Our previous findings (Kanda et al 1992) and those of Gross et al (1979) indicated that nifedipine dilates resistance vessels and increases blood flow, especially coronary blood flow, in conscious dogs. However, the rate-pressure product was not changed significantly. Most investigators (Maxwell & Rencis 1973; Toribatake et al 1985; Kimura et al 1986; Kanda et al 1993) have reported that nifedipine fails to reduce oxygen consumption, although in a few studies arterio-venous oxygen differences were reported to be decreased in anaesthetized open-chest dogs (Jolly et al 1981). Moreover, in the conscious state, reflex tachycardia and vasoconstriction may modulate and even counteract the direct effects of nifedipine. Another problem that could potentially limit nifedipine's application in heart failure is the apparent lack of balanced effects on preload reduction (Kubo et al 1985).

In the present study, NT-1 and nifedipine in combination decreased blood pressure and increased heart rate and coronary blood flow to greater extents than nifedipine alone, indicating that NT-1 enhances the coronary and systemic vasodilatory actions of nifedipine. Schwartz & Bache (1988) studied the combined effects of intravenous administration of calcium antagonists and nitroglycerin on

large coronary artery diameter in conscious dogs. They reported that at the time of the peak increase in diameter after nitroglycerin administration, aortic pressure, heart rate, and circumflex coronary blood flow had all decreased significantly compared with their values in response to nifedipine alone. They concluded that the effects of nitroglycerin and nifedipine on large coronary diameter are additive, with the combination of nitroglycerin and nifedipine causing greater coronary dilation than nifedipine alone. However, their results also indicated that excessive afterload reduction caused reductions in coronary perfusion pressure and sinus rate. Kubo et al (1985) suggested that the combination of intravenous infusion of nitroglycerin and oral administration of nifedipine will optimize preload reduction and enhance the vasodilatory action of nifedipine in chronic congestive heart failure. Suitable doses and routes of administration must be considered. However, reflex tachycardia was observed with combined administration of NT-1 and nifedipine, and the rate-pressure product was not increased compared with that with nifedipine alone. It is suggested that preload reduction by NT-1 plays an important role in reducing myocardial oxygen consumption.

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