CARDIOVASCULAR EFFECTS OF DOBUTAMINE, DOPAMINE
AND ISOPROTERENOL ON THE WHOLE ANIMAL
AND ISOLATED CROSS-PERFUSED ATRIUM IN DOGS

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Accepted September 10, 1982

Abstract—The right atrium of the dog was isolated and cross-perfused with arterial
blood of another (donor) dog anesthetized with pentobarbital. When dobutamine,
dopamine or isoproterenol was administered intravenously to the donor dog, the following
changes were elicited in them: Dobutamine caused slight biphasic changes in heart rate.
Dopamine induced biphasic changes in blood pressure and heart rate. Isoproterenol
produced a decrease in blood pressure and a marked increase in heart rate. All these 3
catecholamines, however, induced positive chronotropic and inotropic effects in a similar
fashion on the isolated atrium cross-perfused with blood of the donor dog. When
injected into the cannulated sinus node artery of the isolated dog atrium, dobutamine,
dopamine or isoproterenol induced monophasic positive chronotropic and inotropic
effects in a dose-related manner, although the potency of each of the drugs was different.
Dobutamine-induced effects were abolished by propranolol, but not modified by imi-
pramine which suppressed significantly tyramine- and dopamine-induced effects. The
difference in dobutamine-induced chronotropic effect between the whole animal and
the isolated atrium may be due mainly to modification by extracardiac factors in the whole
animal.

Dobutamine is a synthetic catecholamine
developed by Tuttle and Mills (1) to provide
a clinically more useful inotropic agent
having less side effects. Indeed, dobutamine
directly increases myocardial contractility
without inducing marked tachycardia or
greatly changing peripheral arterial resistance
in intact dogs (1–3). In the cat papillary
muscle, dobutamine increases the con-
tractility more but the automaticity less than
did isoproterenol (1). However, no report is
available concerning the effect of dobutamine
assessed in isolated dog heart preparations.
Thus, in the present study, we attempted to
compare chronotropic and inotropic effects of
dobutamine, dopamine and isoproterenol
using the isolated dog atrial preparation which
was perfused with the arterial blood of the
donor dog (4, 5). We administered these
three catecholamines intravenously to the
donor dog or intraarterially to the isolated
atrium to observe their direct cardiac chrono-
tropic and inotropic effects and probable
modification of these effects by extracardiac factors.

Materials and Methods

Twenty mongrel dogs weighing 11–25 kg
were anesthetized with sodium pentobarbital
(30 mg/kg, i.v.). The right atrium was
quickly removed and immersed in Tyrode
solution at 4–10°C. The right atrium was then
perfused with blood from the carotid artery
of a heparinized donor dog. Perfusion
pressure was kept constant at 100 mm Hg. The atrium which was usually subjected to a resting tension of 2 g was suspended in the bath filled with blood maintained at a constant temperature of 37°C. Atrial rate and isometric tension development of the isolated atrium and systemic blood pressure and heart rate of the donor dog were simultaneously measured during the experiments. The details of the preparation are described in previous papers (4, 5).

Drugs used in the present study were dobutamine hydrochloride (Shionogi Co. Ltd.), dopamine hydrochloride (Tokyo Kasei), isoproterenol hydrochloride (Nikken Kagaku), imipramine hydrochloride (Fujisawa), tyramine hydrochloride (Wako) and propranolol hydrochloride (Sumitomo Chemicals). Each drug solution was injected by 2 different ways, i.e., intravenously to the donor dog or intraarterially to the sinus node artery of the isolated atrium in a volume of 0.01-0.03 ml.

Results

Effects of intravenous administration of dobutamine, dopamine and isoproterenol on the intact dog and isolated atrium: When injected into the jugular vein of the donor dog, dobutamine (3–10 µg/kg) produced a monophasic increase in systemic blood pressure usually accompanying an increase in heart rate. At 30 µg/kg, an increase in blood pressure was not monophasic, and two peaked responses were frequently observed. The chronotropic responses were also biphasic with this dose. At the same time, only monophasic positive chronotropic and inotropic responses were usually observed in the isolated atrium which was perfused with donor’s arterial blood. Figure 1 shows one such experiment. On the other hand, dopamine (10–100 µg/kg, i.v.) produced greater changes in blood pressure of the donor dog, although changes in sinus rate

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Fig. 1. Effects of dobutamine injected into the jugular vein of a donor dog at doses of 3–30 µg/kg on the systemic blood pressure and heart rate in a donor dog (A) and the developed tension and atrial rate in an isolated atrium (B). The isolated atrium was perfused with arterial blood led from the donor dog.
and developed tension of the isolated atrium were smaller than those produced by dobutamine. Isoproterenol (0.03–0.3 μg/kg, i.v.) caused a decrease in blood pressure and an increase in heart rate of the donor dog. Every examined drug produced similar response patterns in the isolated atrium. Summarized data are shown in Fig. 2.

![Graphs showing effects of drugs on blood pressure and heart rate](image)

**Fig. 2.** Effects of dobutamine, dopamine and isoproterenol administered into the jugular veins of donor dogs at increasing doses of each compound in each of 7 experiments. The control blood pressure and heart rate in donor dogs were 95±8 mm Hg and 145±10 beats/min, respectively, and the developed tension and sinus rate in isolated atria were 2.0±0.2 g and 102±8 beats/min (mean±S.E.M.), respectively. Vertical lines represent the standard errors of the mean. Solid lines show values of maximum positive effects, and dotted lines show those of maximum negative effects.

![Graphs showing chronotropic and inotropic effects](image)

**Fig. 3.** Positive chronotropic and inotropic effects of isoproterenol, dopamine and dobutamine injected into the cannulated sinus node artery of an isolated atrial preparation.
Effects of intraarterial injection of dobutamine, dopamine and isoproterenol into the sinus node artery of the isolated atrium: When injected into the cannulated sinus node artery of the isolated atrium, dobutamine (0.1–1.0 µg) induced positive chronotropic and inotropic effects dose-relatedly. Dopamine (0.1–3.0 µg) and isoproterenol (0.003–0.03 µg) also induced positive responses in a dose-related manner. The responses to the three compounds were similar in pattern, and there were differences only in their potencies. A series of experiments is shown in Fig. 3. Summarized data are shown in Fig. 4. These effects were abolished after i.a. injection of 10 µg of propranolol in 2 experiments.

Effects of imipramine on responses to dobutamine, dopamine and tyramine: When injected into the sinus node artery, imipramine induced long-lasting positive chronotropic and inotropic responses following brief negative ones, as reported previously (6). Positive inotropic and chronotropic responses to tyramine were significantly suppressed after i.a. injection of 30 µg of imipramine. Dopamine-induced positive inotropic and chronotropic responses were also suppressed by this dose of imipramine to a lesser extent than the tyramine-induced ones. On the other hand, dobutamine-induced responses were not influenced by imipramine. A typical experiment is in Fig. 5, and summarized data are shown in Fig. 6.

Fig. 4. Effects of isoproterenol, dobutamine and dopamine on sinus rate and contraction in 5 isolated dog atria. Vertical lines represent the standard errors of the mean.

Fig. 5. Effects of imipramine on dobutamine- and tyramine-induced cardiac actions in an isolated atrium.
Fig. 6. Effects of imipramine on actions of dobutamine, dopamine and tyramine in 5 isolated dog atria.

Fig. 7. Ratios of positive inotropic (PIE) and positive chronotropic effects of 10 kinds of substances in isolated and blood-perfused dog atria. Isop: isoproterenol, NE: norepinephrine, EPI: epinephrine, Dob: dobutamine, Ty: tyramine, and Dbc: dibutyryl cyclic AMP.

Discussion

An i.v. administration of dobutamine to an intact animal produces a lesser increase in systemic blood pressure than that of dopamine (1, 2). However, in isolated atria which were perfused with donor’s blood, an i.v. injection of dobutamine to the donor dog caused more potent positive chronotropic and inotropic effects than that of dopamine. Moreover, an intra-arterial injection of dobutamine to the isolated atrium caused more potent chronotropic and inotropic effects than that of dopamine, with essentially the same pattern of response as that to isoproterenol. In isolated atrial preparations, the ratio of the inotropic effect to the chronotropic effect for each dose of the drugs was studied in our previous reports (7-10). Figure 7 shows the ratio for dobutamine determined in the present study as well as the ratios for other drugs determined in both present and previous studies. Glucagon showed an obviously selective chronotropic action (7) and N-glycylglycylleucyl-dopamine a relatively selective inotropic action (10). However, dobutamine shows a ratio similar to dopamine, norepinephrine, epinephrine or dibutyryl cyclic AMP, indicating that these compounds have no selective inotropic action on the isolated heart preparation. Compared with the ratio for dobutamine, the ratio for isoproterenol is slightly larger and that of tyramine is smaller, but insignificantly.

Tuttle et al. (11) reported that for an equivalent inotropic effect on papillary muscle, isoproterenol had a greater chronotropic effect than dobutamine on spontaneously beating right atrial strips in the cat. On the other hand, Bodem et al. (12) failed to find an inotropic/chronotropic difference between isoproterenol and dobutamine on isolated cat papillary muscles and rat atria, although they used their preparations at a relatively low temperature of 30°C. Tuttle et al. (11) thought that in the heart with intact circulation, agonists are delivered through the vasculature, and diffusion distances from the capillaries to the sites governing chronotropic and inotropic responses are similar; but in vitro access to the receptor sites is by simple diffusion from the bathing fluid, and diffusion distances are not equal. The atria are thin, and the sinoatrial cells that determine the chronotropic response are close to the surface. For this reason, they have considered that in
isolated tissues, chronotropic responses are elicited more readily than inotropic responses. In the present experiments, however, we used isolated dog atrial preparations which were perfused with arterial blood led from the donor dog, and each of the drugs was administered via an intravascular route at a physiological temperature of 37°C. This means that the isolated atrial preparation we employed has good blood perfusion to the receptor sites responsible for chronotropism and inotropism. Therefore, it seems that dobutamine as well as dopamine and isoproterenol has no selective inotropic action. The lower chronotropic effect of dobutamine in the whole animal may be due to influences of extracardiac factors.

In a whole animal, it was reported that dobutamine-induced cardiac effects were not influenced by desmethylimipramine, an uptake blocker of catecholamines (1). In the present study by use of isolated atra, we confirmed that dobutamine-induced positive chronotropic and inotropic effects were not modified by treatment with imipramine, although tyramine-induced ones were markedly suppressed and dopamine-induced ones were slightly but significantly suppressed as reported previously (9). Therefore, it was confirmed that dobutamine, unlike dopamine and tyramine, has no releasing action of norepinephrine.

Recently, Ruffolo et al. (13) demonstrated existence of alpha and beta adrenergic activities in the action of dobutamine and its stereoisomers in vitro. They have reported that the (-)-isomer activates the alpha receptor to produce a response, while the (+)-isomer antagonizes activation of the alpha receptor competitively and that in addition, both stereoisomers of dobutamine are agonists of beta adrenergic receptors in isolated cardiac tissues. Thus, the racemate may exert its action primarily on the heart without marked peripheral vascular actions because the drug is expected to activate the beta receptors without having marked effects on the alpha receptors. It is considered that changes in cardiac function induced by dobutamine in vivo might be modified by extracardiac factors such as reflex mechanisms.

Acknowledgements: We are grateful to the Shionogi Co. Ltd., Japan, for supplying dobutamine hydrochloride.

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