The Dopamine-Induced Coronary Vasoconstrictor Response Is Potentiated by Adenosine Administration in the Dog Heart

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SUMMARY

The ineffectiveness of β-adrenergic blockade in abolishing adenosine-induced coronary vasodilation was utilized to demonstrate that dopamine (DA) is capable of eliciting very strong coronary vasoconstrictor actions in vivo. In 2 separate groups of dogs anesthetized with pentobarbital, responses to DA were assessed either by flowmeter recordings or by computer-aided infrared thermography, which senses coronary blood flow-dependent heat emission from the epicardium. In untreated controls, submaximal DA infusions (16 μg·kg⁻¹·min⁻¹ iv) elicited a coronary vasodilator response. The thermographic equivalent of this hemodynamic action was an increased epicardial temperature. Pretreatment with oxprenolol (0.5 mg·kg⁻¹ iv) preserved both basic heart activity and cardiac heat emission at levels which were comparable to the control state, but prevented DA mediated excitation of cardiac and coronary β-adrenoceptors. In this state, DA infusion constricted the coronary arteries and tended to decrease heat emission. However, both types of effects were moderate, and only the hemodynamic effect was statistically significant. If DA was given after the coronary bed had been dilated submaximally by adenosine (30 μg·kg⁻¹·min⁻¹ infused into the left heart), the flow-reducing effect of DA became a dramatic phenomenon, and the DA-induced epicardial cooling was significantly potentiated. The results show that after eliminating conventional β-effects, DA affects the coronary arteries through vasoconstrictor mechanisms. This finding suggests that the DA-induced constriction is limited in undilated coronary arteries by the metabolic autoregulatory capacity of the vessels.

Additional Indexing Words:
β-Adrenergic blockade Oxprenolol Coronary vascular conductance Thermography Epicardial heat emission
The participation of a competitive vasoconstrictor component in dopamine-induced coronary effects has been emphasized by several workers. This component, which can be unmasked by β-adrenergic blockade, is generally believed to be weak in nature, but by no means is this opinion unanimous. However, the coronary vasoconstrictor potency of dopamine, even in β-blocked hearts, seems to be strongly limited through factors that are connected to the metabolic autoregulatory capacity of the vessels, a phenomenon of outstanding importance in the coronary bed. To overcome this limitation, we tested the pure vasoconstrictor potency of dopamine during the non-metabolically coupled coronary vasodilation elicited by exogenous adenosine. We exploited the original observations of Lammerant and Becsei who described that the primary vasodilator effect of adenosine is unaffected after β-blockade. However, as a secondary action, the nucleoside enhances the coronary adaptation to lower cardiac metabolic demands. In agreement with these findings, Johannsen et al also verified the existence of enhanced sympathetic vasoconstrictor influences in the overperfused coronary bed.

Methods

Fourteen mongrel dogs of either sex, weighing 16–29 kg, were anesthetized with pentobarbital sodium (30–35 mg·kg⁻¹, iv). Artificial ventilation was maintained with a volume-cycled respirator at a rate of 16–18 min⁻¹ using room air. The heart was exposed either through a left thoracotomy in the fourth intercostal space (preparation type I) or through a transverse sternotomy and bilateral fourth intercostal space thoracotomy (preparation type II). The pericardium was opened, and the heart was firmly suspended in a pericardial cradle. A polyethylene catheter was inserted into a femoral artery for measuring aortic blood pressure with a Statham P23 Db transducer. Another catheter was introduced into the left auricular appendage for adenosine infusions. In 8 dogs (type I preparation), the left anterior descending (LAD) coronary artery was dissected free close to its origin and an electromagnetic flow probe (Statham, SP 2202) was fitted around it. Phasic and mean coronary blood flow were recorded simultaneously, the latter variable being obtained by electrical integration. Ventricular inotropism in the LAD-area was assessed with the aid of a Walton-Brodie strain gauge. The myocardial segment between the 2 feet of the gauge was stretched by about 40% of its initial length, thus ensuring the independence of the developed force from the preload and afterload. All hemodynamic variables were displayed continuously on a four-channel Hellige recorder. Heart rate
changes were computed from records taken at high paper speed.

In 6 dogs (type II preparation), telethermograms of the whole anterior cardiac surface were recorded with the aid of AGA 750 Thermovision equipment, and analyzed according to the principles described earlier in detail. This method, as shown by former investigations performed in this laboratory, estimates, by sensing the flow-dependent infrared irradiation from the epicardium, the level and distribution of blood supply. The thermographic images were recorded simultaneously on a video-tape, photographed, and fed to an on-line computer system (M08X). Computerized evaluation was performed for two cardiac subunits: the left (LAD-dependent) and right ventricular areas. By measuring the total extent of these areas (i.e. the number of thermographic samples which was equivalent to about 0.5·10^5 pixels for each image), the temperature profiles (expressed as a percent distribution of isotherms) and the mean temperature (the average of heat emission from the relevant area) could be calculated by the computer program. The sensitivity of detection was chosen so that each isotherm represented a 0.5°C step in temperature. Accordingly, by employing 10 bands of isotherms, it was possible to cover a 5°C range. The experiments were carried out at 24–26°C room temperature and 60–70% relative humidity. The body temperature of the animals was maintained at 37±0.5°C.

Dopamine was diluted in physiologic saline solution and infused iv at a dose of 16 µg·kg^{-1}·min^{-1}. According to earlier findings, this dose elicits maximal cardiostimulation and submaximal coronary vasodilation in controls. β-Blockade was effected by a 0.5 mg·kg^{-1} iv dose of oxprenolol, an agent with intrinsic sympathomimetic activity, thus preserving the control levels of ventricular inotropism and coronary vascular tone. The efficacy of β-blockade was tested as formerly reported. Dopamine infusions were repeated in two subsequent experimental phases after β-blockade: (1) with non-dilated vessels and (2) during the infusion of adenosine (30 µg·kg^{-1}·min^{-1}) into the left auricle. In preliminary experiments, this dose was selected to produce maximal coronary flow increases and near maximal increases of coronary vascular conductance. It was verified that this type of coronary vasodilation can be maintained at a constant level for at least 15 min. In order to obtain steady-state values for dopamine responses, the drug was infused for 3.5–5 min. Hemodynamic variables were chosen for data analysis during the last 30 sec periods of infusions. Hemodynamic coronary responses were characterized by mean flow recordings and percent vascular conductance values (flow/pressure), the resting control level being 100%. A detailed hemodynamic analysis of this preparation is based upon 5/8 dogs which did not exhibit pressor responses to dopamine greater than
+40 mmHg in the control state.

Five type II preparations out of 6 were suitable technically for a correct thermographic analysis. Drug-induced changes were evaluated by mean alterations of flow-dependent epicardial temperature which were computed, in duplicate, every min during the dopamine infusions. Since the exact time course of dopamine-induced warming and/or cooling of the epicardium varied from animal to animal, statistical evaluations were made from maximal and minimal temperature alterations recorded during the infusion periods. Hypertension tended to reduce cooling. To determine dopamine-induced pressor responses (Δ mmHg) necessary to offset a transitory epicardial temperature drop (equivalent to a coronary flow decrease), the time-dependent pressor curves of the dopamine effects were interpolated for Δ0°C values in simultaneously constructed temperature curves. If such a compensation failed to occur (i.e. if the mean temperature remained depressed for the entire infusion period), maximal Δ pressor values were taken for the comparison.

All values quoted in the text, tables and diagrams are mean±SEM. The results were examined statistically using Student’s t-test for paired data. Changes of variables were considered significant when p<0.05.

Results

Hemodynamics:

Figure 1 depicts representative tracings from a typical experiment, while the summarized hemodynamic data during resting conditions and the steady-state changes produced by dopamine are found in Table I. Coronary hemodynamics were explored in a subset of 5 dogs which exhibited only a moderate arterial hypertensive response to dopamine. After treating the preparations with the β-adrenergic blocker oxprenolol, the control parameters of circulatory equilibrium were fairly well preserved. At the same time, as expected, oxprenolol administration virtually abolished the dopamine-induced inotropic and heart rate responses, whereas the coronary response was reversed. However, the dopamine-induced reduction of coronary blood flow after β-blockade was modest. All variables returned rapidly to resting levels when the dopamine infusion was terminated. Thereafter, the dogs were infused with a 30 μg·kg⁻¹·min⁻¹ dose of adenosine. Although upon administering adenosine a slight hypotension ensued, none of the resting levels of hemodynamic variables was significantly altered, except coronary flow which stabilized at a very high rate. At that time, an infusion of dopamine elicited a substantially augmented vasoconstrictor coronary response.

Although the trend towards a dopamine-induced hypertension was not
pronounced in 5/8 animals in the type I group, the changes in vascular conductance were also investigated. Figure 2 depicts the alterations of this variable, calculated from individual values of mean flow and pressure. As
Table I. Pharmacologic Influences on

<table>
<thead>
<tr>
<th></th>
<th>Coronary blood flow (ml·min⁻¹)</th>
<th>Mean blood pressure (mmHg)</th>
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<tbody>
<tr>
<td></td>
<td>R</td>
<td>DA</td>
</tr>
<tr>
<td>A Control</td>
<td>37.5±6.1</td>
<td>+26.1±3.8</td>
</tr>
<tr>
<td>B β-blockade*</td>
<td>32.5±3.1</td>
<td>−3.1±1.1</td>
</tr>
<tr>
<td>C β-blockade+adenosine**</td>
<td>85.8±17.0*</td>
<td>−44.0±9.6**</td>
</tr>
</tbody>
</table>

†: mean values±SEM, n = 5.
R=resting level; DA=dopamine-induced change (p values refer to these changes, NS=not significant).
* p<0.05, ** p<0.01 from control (A).

ADENOSINE (30 μg·kg⁻¹·min⁻¹)

Fig. 2. Statistical evaluation of changes in calculated coronary vascular tone. Percent values of mean vascular conductance (100%=resting control level). Note the reduced scale for coronary reactivity during the vasodilator action of adenosine (right). White columns: resting level. Black columns: during infusion of dopamine (16 μg·kg⁻¹·min⁻¹).

shown, dopamine augmented the vascular conductance by 48.9±9.6% in controls. Pretreatment with oxprenolol converted the vasodilator action of dopamine to a moderate vasoconstriction (from 97.7±8.6% to 86.2±8.4%). However, during adenosine-induced vasodilation the vascular conductance decreased from 266.1±41.2% to 113.0±18.2%. Calculation of the late
Coronary Hemodynamics

<table>
<thead>
<tr>
<th>Heart rate (beats·min⁻¹)</th>
<th>Ventricular force (percent)</th>
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<tbody>
<tr>
<td>R</td>
<td>DA</td>
</tr>
<tr>
<td>159 ±8</td>
<td>+20</td>
</tr>
<tr>
<td>±7</td>
<td></td>
</tr>
<tr>
<td>128** ±8</td>
<td>+3*</td>
</tr>
<tr>
<td>±2</td>
<td></td>
</tr>
<tr>
<td>125** ±6</td>
<td>+5</td>
</tr>
<tr>
<td>±1*</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01 from β-blockade (B).
a: oxprenolol (0.5 mg·kg⁻¹).
b: infusion of adenosine (30 μg·kg⁻¹·min⁻¹).

In 3 dogs, the administration of dopamine elicited blood pressure increases of more than 40 mmHg (see Methods). However, the behavior of the calculated coronary vascular conductance was quantitatively similar to the other 5 dogs in the experimental group. In response to dopamine, coronary vascular conductance (mean) increased by 32.2±8.9% in controls. It decreased from 99.3±10.9% to 86.0±9.4% (p<0.05) after β-blockade, and from 251.7±29.8% to 112.6±11.3% (p<0.05) after β-blockade+adenosine. However, since dopamine enhanced the mean blood pressure by 65±6, 47±8, and 41±8 mmHg in the three consecutive phases of experiments, the decrease in coronary blood flow was apparent only in the third phase. (The corresponding changes were: +27±5, +5±1 and −22±3 ml·min⁻¹.)

**Thermography:**

Since, as noted above, dopamine-induced adrenergic activation may frequently increase the systemic vascular tone and thus the blood pressure, coronary adaptation was investigated by infrared cardiothermography. Data from a representative experiment are given in Fig. 3. During the control phase (A), dopamine administration increased the mean epicardial temperature in both ventricles. This effect was clearly reversed in the third experimental phase during the adenosine infusion (C). In the second phase, after β-blockade without adenosine (B), the dopamine-induced changes were equivocal. The histograms describing the temperature profiles of the ven-
Table II. Pharmacologic Influences on Resting Levels of Epicardial Heat Emission+

<table>
<thead>
<tr>
<th></th>
<th>Mean blood pressure (mmHg)</th>
<th>Mean epicardial temperature (°C)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Left ventricle</td>
</tr>
<tr>
<td>A</td>
<td>Control</td>
<td>121±9</td>
</tr>
<tr>
<td>B</td>
<td>β-blockade&lt;sup&gt;a&lt;/sup&gt;</td>
<td>112±6</td>
</tr>
<tr>
<td>C</td>
<td>β-blockade+adenosine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>94±4*#</td>
</tr>
</tbody>
</table>

*: mean values for resting levels±SEM, n=5.
* p<0.05 from control (A).
# p<0.05 from β-blockade (B).
a: oxprenolol (0.5 mg·kg<sup>-1</sup>).
b: infusion of adenosine (30 μg·kg<sup>-1</sup>·min<sup>-1</sup>).

Tricles revealed comparatively compact blocks of isotherms during the whole course of interventions. At the same time, the histograms revealed some unpredicted changes in the contours of these blocks. Since earlier thermographic analyses determined that cardiac temperature is a monotonic function of blood flow, these alterations can be interpreted as moderately inhomogenous responses of myocardial blood supply which are characterized by distinct mean temperature changes for each ventricle. In agreement

Fig. 3. Representative thermographic experiment. A, B, C and 1, 2, 3 as indicated in the panel of blood pressure (below). Left panel: cardiac telethermograms (pseudocolored images in the original). Right upper panel: computerized evaluation of thermograms. Each column of histograms represents an isotherm of 0.5°C. Arrowheads denote mean temperature. Shift of mean values from left to the right: cooling of the epicardial surface. Right lower panel: changes in blood pressure.
with this interpretation, the resting level of epicardial temperature was consequently less in the right ventricle. Adenosine, but not oxprenolol, modified the level of this variable in both ventricles (Table II).

Since adaptation to dopamine-induced increases in coronary driving pressure implies a correlated shift of flow-dependent heat emission over a given temperature range, thermographic responses to dopamine were characterized statistically by minimal and maximal $J$ values of mean temperature

![Graphs showing thermographic responses to dopamine](image)
Fig. 4. Dopamine-induced changes in mean epicardial temperature. Minimum and maximum values as determined with computer-aided thermography during each minute of drug-infusion were selected to characterize coronary adaptation.

Table III. Mean Blood Pressure Increase (mmHg) Necessary for the Compensation of Epicardial Cooling

<table>
<thead>
<tr>
<th></th>
<th>β-blockadea</th>
<th>β-blockade+ adenosineb</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td>+33.0±15.4</td>
<td>+98.4±20.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>+30.6±11.7</td>
<td>+98.0±24.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*a*: mean values±SEM, n=5.

*b*: infusion of adenosine (30 µg·kg⁻¹·min⁻¹).

P values refer to changes during adenosine infusion.

during the process of adaptation (Fig. 4). After β-blockade, and especially after β-blockade+adenosine, highly significant changes were observed in both temperature minima and maxima. These changes were evidently analogous to the flow changes measured in hemodynamics. In the control phase, only temperature increases were observed after administration of dopamine. After β-blockade, most of the responses became biphasic: epicardial cooling was followed by adaptive temperature increases which were more or less synchronous with the progressive increases of blood pressure.
During the vasodilator action of adenosine, the cooling response was accentuated and the warming was attenuated. Moreover, during the action of adenosine, higher pressure changes were needed to overcome epicardial cooling than in the preceding experimental phase (Table III).

**DISCUSSION**

These data confirm earlier results\(^7\),\(^13\) that dopamine administration after \(\beta\)-adrenergic blockade will invariably cause coronary vasoconstriction in the dog heart. This is in sharp contradistinction with the assumption of Rajfer and Goldberg\(^14\) who stated that "dopamine-induced vasodilation of the renal, mesenteric, coronary,\(^*\) and cerebral vascular beds is attributed to the activation of DA\(_1\) vascular receptors". Reasons have recently been given\(^7\) why this assumption, which was deduced from ambiguous effects of intracoronary or intravenous dopamine boluses\(^3\),\(^15\),\(^16\) and irrelevant observations made on isolated coronary strips\(^3\),\(^17\) underestimates the role of \(\beta\)-adrenergic activation and the competition with \(\alpha\)-activation in the dopamine-induced coronary effects. To obtain clear evidence of the coronary vasoconstrictor response to dopamine, the drug must be administered as a continuous infusion.\(^7\),\(^13\)

A significant finding made in this investigation was that the vasoconstrictor action was more intense during adenosine-induced coronary vasodilation. Similar results were obtained by Johannsen et al\(^9\) with cardiac sympathetic nerve stimulation, norepinephrine and phenylephrine. Thus, dopamine may be a highly relevant model-drug to gauge the width of catecholaminergic coronary vasoconstriction, a response not apparent under ordinary circumstances. Since the pioneering studies of Szentiványi and his associates on coronary vasoconstriction mediated through cardiac sympathetic fibres\(^3\),\(^18\),\(^19\) a great body of experimental and clinical evidence has been provided for the multifactorial nature of influences that determine, during adrenergic stimulation, the range of coronary flow decreases and resistance increases, respectively.\(^20\) It seems that one of the most important factors offsetting coronary vasoconstriction during sympathetic stimulation is the simultaneous increase of cardiac metabolic demands coupled to \(\beta\)-adrenergic activation. Adenosine has been reported to decrease rather than increase the metabolic demands of the heart.\(^21\),\(^22\) In this study, the relative vasoconstrictor range of dopamine was found to be at least as great as the coronary vasodilator range determined with blocked \(\alpha\)-adrenoceptors in car-

\(^*\) our italics
lier investigations.\textsuperscript{7,13} Although myocardial $O_2$-consumption was not measured, it seems safe to conclude that the $O_2$-consumption sparing effect of adenosine was directly related to the potentiated vasoconstriction.

While the lack of great increases in blood pressure during the dopamine action was certainly important in obtaining unequivocal evidence for the vasoconstrictor effect, the total absence of dopamine-induced arterial hypertension is a comparatively rare occurrence in the dog. However, the potentiation of the dopamine-induced coronary vasoconstriction during adenosine administration was very pronounced, even in preparations which responded with a considerable pressor action to dopamine. This conclusion was also reinforced by the analogous thermographic reactions: dopamine-induced cooling of the epicardial surface, a phenomenon dependent on, and equivalent to drug-induced coronary vasoconstrictor responses,\textsuperscript{10,11} was significantly potentiated by adenosine. Moreover, the cooling effect was compensated by a much greater hypertensive dopamine action when the animals were subjected to vasodilation by adenosine infusion. In fact, all of the essential conclusions derived from hemodynamic studies were confirmed by direct thermographic visualizations. This technique, as developed by Papp et al, has proven to be a very convenient tool for demonstrating some characteristic features of coronary vascular alterations, especially their homogeneity.\textsuperscript{10,12} It seems that as far as the epicardial distribution of flow over the left and right ventricular surfaces is concerned, dopamine actions that are not totally homogeneous can be verified with the aid of thermography. Since the thermographic camera only detects blood supply to the outer myocardial layer, further investigations are needed to determine whether a transmural redistribution in coronary flow has any role in these phenomena.

References


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