THE EFFECT OF CARDIAC SYMPATHETIC NERVE STIMULATION ON THE RIGHT VENTRICLE IN CANINE HEART

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The change in coronary hemodynamics during right or left cardiac sympathetic nerve stimulation was studied in anesthetized open chest dogs. No difference in the increasing rate of mean coronary blood flow between right coronary artery (RCA) and left anterior descending coronary artery (LAD) was observed. However the increasing rate of right ventricular systolic pressure x heart rate (RVSP x HR) was greater than that of left ventricle (LV). With phentolamine injection, cardiac sympathetic nerve stimulation showed similar changes as the controls. Beta-stimulation by isoproterenol infusion did not cause different effects on the increasing rate of coronary blood flow between RCA and LAD. These results showed that cardiac sympathetic nerve stimulation increased the double product of the right ventricle (RV) more than that of the LV and the increase was not affected by phentolamine. Moreover, cardiac sympathetic nerve stimulation, either the right or the left, caused the greater effects on the RV compared to the LV mainly through beta-adrenoceptors, and that the response of the RV to increase in oxygen demand was possibly, in part, different from that of the LV.

The effect of changes in cardiac sympathetic nerve tone on coronary circulation is shown as result of the integration of the direct effect on coronary artery and the effect through myocardial metabolic changes. Beta2-mediated-vasodilation plays a minor role in coronary circulation from a physiological point of view and the direct control of the sympathetic nerve may come mainly from alpha-mediated vasoconstriction. In the right coronary artery the blood flow proportion of systole to diastole is one half, resulting in a blood flow pattern different from the left coronary artery. Furthermore, the sympathetic nerve stimulation, which elevates intraventricular pressures, could affect the right ventricle differently from the left ventricle. It is known that the difference in intraventricular pressure accounted for the different flow patterns of two coronary arteries. Thus, ventricular pressure change caused by the cardiac nerve stimulation could contribute to modify coronary blood flow pattern. In this study, we attempted to determine the different responses of RCA and LAD to the cardiac sympathetic nerve stimulation in the mongrel dogs, and also to clarify the relationship between right coronary blood flow and right ventricular oxygen demand in the presence and absence of alpha-adrenergic blockade. Finally, intravenous infusion of isoproterenol (ISP) was administered to examine postsynaptic beta-adrenergic effect on blood flow in the RCA and LAD.

Key words:
Beta-adrenergic effect
Right ventricle
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Isoproterenol
Coronary blood flow

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METHODS

Healthy mongrel dogs, each weighing from 12 to 26 kg, were anesthetized using pentobarbital sodium (25–30 mg/kg iv). Artificial ventilation with a mixture of room air and 100% oxygen was provided by a Harvard respirator. Intravenous infusion of 7% sodium bicarbonate solution and changing tidal respiratory volume or oxygen ratio in air maintained arterial PH, PO2, and PCO2 within the normal ranges. PH, PO2, and PCO2 were measured by a Corning model 165/2 gas analyzer.

Midsternotomy and the construction of a pericardial cradle exposed the heart for the implantation of electromagnetic flow probes and pneumatic occlusive cuffs on the proximal right coronary artery and the left anterior descending coronary artery distal to the conus branch. The catheters were inserted through right carotid artery into ascending aorta, and through apex into the right and the left ventricle to serve for blood pressure monitoring. Hemodynamic data were recorded continuously during the course of the experiment using a Siemens-Elema Mingograph model 804 (West Germany) at the paper speed of 2.5 mm/sec or 100 mm/sec. The right and the left stellate gangions were torn off, and a bipolar electrode was fitted to anterior or posterior subclavian ansa for stimulation of the nerve. For estimating coronary reactivity, reactive hyperemia following 15 seconds of coronary occlusion was observed. When the peak reactive hyperemia was less than 300% of baseline control, data from the dog hearts were not used for analysis. After hemodynamic steady state was achieved, the right or the left sympathetic nerve was stimulated by an electronic stimulator (Nihon-Koden model MSE-20) at 20Hz, 10 volts for 30 seconds. The change in coronary hemodynamics was observed, and then hemodynamic measurements allowed to return to the control for at least 10 min. The right or left nerve stimulation was done unintentionally. Five dogs received intravenous infusion of phentolamine at a rate of 0.1 mg/kg/min. In order to estimate the completeness of alpha-receptor blockade, methoxamine (0.2 mg/kg) was administrated intravenously. Five minutes later hemodynamic state became stable, and a similar procedure of nerve stimulation was repeated.

Another five dogs received intravenous infusion of ISP at a rate of 0.1 µg/kg/min, and the change in coronary hemodynamics was observed.
Before and after nerve stimulation and ISP infusion, flow zero was determined by inflating pneumatic occluder cuff. On completion of the entire series, injection of Evans blue and neutral red solution into the RCA and the LAD, respectively, delineated the myocardium under study. The weight of dye-stained myocardium served to standardize blood flow per 100 grams of tissue. Statistical analysis within groups was made by paired Student's t-test. Differences were considered significant when value was less than 0.05. Group data are presented as mean \pm SEM.

RESULTS

1) The change in hemodynamics during right (RCSNST) and left cardiac sympathetic nerve stimulation (LCSNST) (Table I).

Coronary blood flow began to increase 3–4 seconds after RCSNST started, reached the maximum flow rate at 20–30 seconds (average 27 ± 3 seconds), and maintained this flow level or decreased slightly during the stimulation. During RCSNST, blood flow in RCA and LAD increased to about 101% and 79%, respectively above the controls, and at the same time the vascular resistance decreased by about 38% and 34%, respectively. Statistical analysis revealed that the difference of coronary blood flow between RCA and LAD was not significant (Fig. 1). Heart rate, mean aortic pressure, right (RVSP), and left ventricular systolic pressure (LVSP) increased by about 38%, 12%, 63% and 10%, respectively. LCSNST began to increase coronary blood flow at 3–4 seconds, and the flow came to its peak at 19–30 seconds (average 24 ± 4 seconds), followed by an almost constant flow rate. The peak flow rate in RCA and LAD were about 81% and 80%, respectively, which is greater than the controls while vascular resistance decreased by 33% in RCA and by 32% in LAD. The responses of two coronary arteries were not statistically significant (Fig. 1). Heart rate, mean aortic pressure, RVSP, and LVSP increased about 17%, 14%, 79% and 18%, respectively. In either RCA or LAD, there was no significant difference in increasing rate of coronary blood flow between RCSNST and LCSNST.

2) The change in RVSP × HR and LVSP × HR during RCSNST and LCSNST (Fig. 2).

During RCSNST RVSP × HR and LVSP × HR,
### Table II Changes of Heart Rate and Cardiac Cycle During Right or Left Cardiac Sympathetic Nerve Stimulation

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>Duration of systole (msec)</th>
<th>Duration of diastole (msec)</th>
<th>D/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>103 ± 7</td>
<td>260 ± 7</td>
<td>317 ± 27</td>
<td>1.22 ± 0.07</td>
</tr>
<tr>
<td>RCSNSSt</td>
<td>170 ± 8**</td>
<td>153 ± 15**</td>
<td>194 ± 12*</td>
<td>1.32 ± 0.19</td>
</tr>
<tr>
<td>Control</td>
<td>105 ± 8</td>
<td>281 ± 16</td>
<td>301 ± 31</td>
<td>1.07 ± 0.10</td>
</tr>
<tr>
<td>LCSNSSt</td>
<td>143 ± 12*</td>
<td>174 ± 6**</td>
<td>260 ± 24</td>
<td>1.49 ± 0.12</td>
</tr>
</tbody>
</table>

n = 4. D/S, the ratio of diastolic duration to systolic duration. *p < 0.05, **p < 0.01. Others are same as in Table I.

![Graph showing changes in coronary blood flow during right or left cardiac sympathetic nerve stimulation.](image)

**Fig.3.** % changes of coronary blood flow in each cardiac cycle during right or left cardiac sympathetic nerve stimulation. *p < 0.05.

Indexes of myocardial oxygen consumption of RV and LV increased by 150% and 65%, respectively, and LCSNSSt increased the indexes by 125% and 45%, respectively. Both RCSNSSt and LCSNSSt increased the double product of RV more than that of LV.

3) The pattern of coronary blood flow during RCSNSSt and LCSNSSt

By measuring the duration of stroke systole and stroke diastole from coronary blood flow pattern, it was found that RCSNSSt shortened stroke systolic and diastolic time together with increment of HR. The ratio of stroke diastolic to stroke systolic time did not change significantly from 1.22 ± 0.07 to 1.32 ± 0.19. While, the duration of stroke systole shortened significantly during LCSNSSt, the stroke diastolic time was unchanged, resulting in an increase in the ratio of stroke diastolic to stroke systolic time from 1.07 ± 0.10 to 1.49 ± 0.12 (Table II). Using Goodman’s medical graphics analyzer (Nagoya, Japan) we measured the stroke systolic and diastolic flow volume from coronary blood flow tracing (Fig. 3). During RCSNSSt, the systolic, diastolic, and total flow volume of a heart beat in RCA decreased, while in LAD the parameters did not change. An end-systolic retrograde-flow of LAD during RCSNSSt appeared in only one dog.

TABLE III 
EFFECTS OF PHENTOLAMINE ON HEMODYNAMIC CHANGES DURING RIGHT OR LEFT CARCIO SYMPATHETIC NERVE STIMULATION

<table>
<thead>
<tr>
<th></th>
<th>Before phenotolamine</th>
<th>Control</th>
<th>After phenotolamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR beats/min</td>
<td>104 ± 10</td>
<td>104 ± 8</td>
<td>104 ± 8</td>
</tr>
<tr>
<td>LVSP mmHg</td>
<td>117 ± 10</td>
<td>167 ± 4</td>
<td>177 ± 8</td>
</tr>
</tbody>
</table>

4) The effect of RCSNST and LCSNST during phenotolamine infusion

After intravenous injection of phenotolamine, mean aortic pressure and LVSP decreased by 25% and 19%, respectively, from the control, but there were no significant changes in HR, RVSP, and blood flow of RCA and LAD. The vascular resistance decreased by 17% in RCA, and by 14% in LAD. With phenotolamine, hemodynamic changes caused by RCSNST or LCSNST were almost the same as changes in the absence of phenotolamine (Table III). As illustrated in Fig. 4, phenotolamine did not significantly affect the increasing rate of coronary blood flow of RCA and LAD which was caused by RCSNST or LCSNST. The vascular resistance of RCA was decreased significantly by RCSNST or LCSNST with phenotolamine infusion. While phenotolamine showed no significant effects on the decreasing rate in LAD. Changing rate of coronary blood flow and coronary vascular resistance were not different between RCA and LAD during RCSNST and LCSNST. RVSP x HR and LVSP x HR with phenotolamine increased by 87% and 50%, respectively, with RCSNST, and by 179% and 83%, respectively, with LCSNST. The increasing rate of RVSP x HR with RCSNST and LCSNST was significantly greater than that of LVSP x HR.

5) Ratio of change in RVSP x HR to that in LVSP x HR during RCSNST and LCSNST

To examine the different effect of beta-adrenoreceptor stimulation of RCSNST to the ventricles from that of LCSNST, we compared the % change ratio of RVSP x HR to LVSP x HR during RCSNST with that of LCSNST after blocking alpha-adrenoreceptors by phenotolamine. The ratio was 10.3 ± 3.1 during RCSNST, and tended to be higher than the index during LCSNST (2.8 ± 1.1, p < 0.10).

6) Hemodynamic changes during intravenous infusion of ISP

During ISP infusion HR and RVSP significantly increased. Blood flow of RCA and LAD increased by 97% and 108%, respectively with no significant difference between increasing rate of RCA and LAD. Vascular resistance decreased by 59% in RCA and 57% in LAD. There was no significant difference between them (Fig. 5).
**DISCUSSION**

In the present study, cardiac sympathetic nerve stimulation increased the product of heart rate and systolic pressure which is an index of ventricular myocardial oxygen consumption. The increase was greater in the right ventricle than in the left ventricle. At the same time, there was no significant difference in blood flow increments between the right and the left coronary artery. These effects of the stimulation were similar for both the right and left cardiac nerves. Pretreatment with phentolamine did not affect the findings, and isoproterenol infusion produced similar changes in the double product and coronary flow as the results obtained by the sympathetic nerve stimulations. The myocardial oxygen consumption of right ventricle correlates directly with the product of heart rate and systolic ventricular pressure as of the left ventricle. These results indicate that the cardiac nerve stimulation, of both the right and the left, augments the right ventricular oxygen consumption more than the left through beta-adrenergic stimulation, and alpha-mediated vasoconstriction does not modify the relationship. It is reported that during RCSNS1 or LCSNS1, positive inotropic response of the right ventricular conus and the

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region of coronary sinus is stronger than that of right ventricular posterobasal area and the left ventricle, and that myocardial norepinephrine content of the right ventricle is equal to or larger than that of the left ventricle. When coronary blood flow increased to the maximum level, it passed approximately 25 seconds after starting the stimulation. At that time aortic pressure and heart rate obviously increased, which should increase myocardial oxygen demand of the right and the left ventricles. Furthermore, it is quite likely that during the cardiac sympathetic nerve stimulation beta-adrenergic mediated inotropic action on the myocardium made a greater contribution to the increase in myocardial oxygen demand.

The present study, however, indicated that either the right or the left cardiac nerve stimulation increased ventricular oxygen demand in the right ventricle greater than that in the left, while blood flow increment in the RCA did not differ from the LAD flow increment. The different response of myocardial oxygen demand and coronary flow between the two ventricles to nerve stimulation would account for the different response of the two ventricles to an increase in myocardial oxygen demand. Furthermore our results demonstrated that increases in LAD flow with no increase in oxygen extraction accounted for enhanced oxygen consumption of the left ventricle due to pacing, isoproterenol, or methoxamine and that pacing, isoproterenol, or constriction of the pulmonary artery increased oxygen consumption of the right ventricle by augmented oxygen extraction and a rise in right coronary blood flow. That is, myocardial oxygen extraction increased in the right ventricle together with an increasing coronary blood flow in association with a rise in myocardial oxygen demand, while left ventricular myocardial oxygen extraction remained constant. Therefore, it would appear that, during cardiac sympathetic nerve stimulation, greater increase in oxygen demand by the right ventricle was met by a joint action of increase in oxygen extraction and coronary blood flow, whereas the left ventricular oxygen extraction remained constant.

During LCSNSt the ratio of stroke diastolic to systolic time increased significantly, but RCSNSt did not affect the ratio. And the product of ventricular systolic pressure and heart rate suggested that the effect of right and left ventricular oxygen consumption during RCSNSt was different from LCSNSt. A few reports, including papers of Gregg and Ross are available on how sympathetic nerve stimulation changes coronary blood flow of right ventricle. Gregg et al reported that, during sympathetic nerve stimulation, blood flow of RCA increased to a lesser extent than the blood flow of LAD. They also observed that stroke diastolic flow volume of RCA increased and stroke systolic flow volume decreased or remained constant. However, their study did not estimate the flow pattern in detail because of methodologic limitations: they used rotameter or orifice meter to measure coronary flow, and coronary artery used was perfused by extracorporeal circulation. On the other hand, Ross et al observed similar changes in coronary flow pattern as we did, by measuring blood flow of RCA, LAD and the left circumflex coronary artery simultaneously by electromagnetic flow meters during LCSNSt and LCSNSt. The different effects on coronary flow patterns of LCSNSt and RCSNSt have not been explained clearly. It is known that LCSNSt caused a stronger positive inotropic effect compared with RCSNSt, while a positive chronotropic effect is stronger in RCSNSt. Thus, a possible explanation is that LCSNSt, compared with RCSNSt, augmented myocardial contractility more intensively, resulting in shortened systolic time and relatively longer diastolic time. The longer diastole would be one reason why stroke diastolic flow volume of both RCA and LAD increased significantly during LCSNSt. On the contrary, a more intensive increase in heart rate by RCSNSt caused a decrease in the ratio of stroke diastolic to stroke systolic time. The decreased ratio would be responsible for a fall in stroke diastolic coronary flow. Therefore, RCSNSt and LCSNSt had different effects on coronary blood flow pattern possibly through different innervation to the myocardium.

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