ENDOGENOUS AND EXOGENOUS CATECHOLAMINES CAN ACCENTUATE MYOCARDIAL ISCHEMIA ONLY WHEN CORONARY BLOOD FLOW IS BELOW A CRITICAL LEVEL

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Seventy-eight dogs with graded constriction of the left main coronary artery were studied to determine the coronary blood flow at which the heart is vulnerable to catecholamine induced ischemia.

The left main coronary artery was cannulated with a Griggs' type self-perfusing cannula. The coronary blood flow (CBF) was reduced by graded constriction of the extra-corporeal circuit connected with this cannula. Blood flow rates between 12 and 117 ml/min/100g were studied. Cardiac activation was achieved by either intracoronary administration of a physiological dose of catecholamine (noradrenaline; 0.4 µg/kg/min or adrenaline; 0.2 µg/kg/min), or by electrical stimulation of the left stellate ganglion (4 Hz, 2 msec, 10 V for 5 min). When CBF was below 30 ml/min/100g, accentuated myocardial ischemia was always indicated by lactate production, myocardial creatine phosphate depletion, ischemic ST segment changes, and elevated left ventricular end diastolic pressure (LVEDP) during these stimulations. When CBF was above 50 ml/min/100g, catecholamine clearly accelerated the cardiac function and myocardial metabolism with no sign of ischemia. When CBF was between 30 and 50 ml/min/100g signs of accentuated myocardial ischemia appeared during catecholamine activation in only ½ of the dogs. This study indicated that the critical level for CBF at which endogenous or exogenous catecholamine can produce ischemia is between 30 and 50 ml/min/100g.

AUGMENTATION of cardiac sympathetic nerve activity increases cardiac function and myocardial metabolism in the heart with slight to moderate coronary artery stenosis1–4. In that with more severe stenosis, sympathetic stimulation produces myocardial ischemia3–8. As reported previously, the beneficial or deleterious effects of intravenously infused catecholamine on the ischemic heart have been thought to depend on the perfusion pressure9, myocardial blood flow10 or the intensity and duration of the stimulations11.

In this study we aimed to determine the exact range of coronary blood flow within which catecholamine can produce deleterious effects in the ischemic heart.

We achieved this goal by either infusing catecholamine into the coronary artery or by electrical stimulation of the left stellate ganglion for a relatively long period (5 min), using a global ischemic heart model in which aortic pressure was stabilized.

MATERIAL AND METHODS

Seventy-eight mongrel dogs of either sex
ranging from 10 to 20 kg were anesthetized with sodium pentobarbital, 30 mg/kg, administrated intravenously. The heart was exposed by a bilateral thoracotomy cutting the sternum. The dogs were ventilated with room air from a Harvard respirator.

Arterial PO₂, PCO₂, and pH were measured and were adjusted to be within normal limits during the experiments.

The left main coronary artery was exposed and a ligature was passed under its origin in preparation for cannulation. Ten thousand units of heparin was administrated intravenously to prevent clotting in the perfusion line, and supplemented with 3000 units per hour.

Figure 1 shows the scheme of animal preparations. The left main coronary artery was cannulated with a double lumen cannula with extracorporeal loop via brachiocephalic artery as described by Griggs. Arterial blood from the root of the aorta passed through an electromagnetic flow transducer (Nihon Koden Medical Industry, MF 26) and into the left main coronary artery.

Coronary pressure was measured by a pressure transducer (Nihon Koden M.I., MPU-05) positioned at the level of the left atrium.

A polyethylene cannula was inserted into the coronary sinus, via the right atrial appendage, and was connected through a 3 way stopcock to the left subclavian vein to facilitate coronary sinus blood sampling. A catheter was inserted via the right femoral artery into the arch of the aorta for measurement of the arterial blood pressure. Left ventricular pressure was measured through a short polyethylene cannula connected to a pressure transducer through the left anterior ventricular wall.

The CBF, pressure, and an electrocardiogram from the standard limb lead II were simultaneously recorded on a 8-channel recorder (Nihon Koden M.1, RM-85). ECG-ST was measured after 0.1 mV calibration was performed. The coronary vascular resistance (CVR) was calculated by dividing the coronary diastolic pressure by CBF. Heart rate and ST segment deviation, which was measured 0.06 sec after the end of the QRS complex, were determined from the electrocardiogram. Blood samples were obtained simultaneously from the aorta and the coronary sinus, and oxygen content, hemoglobin and lactate were measured. Immediately after blood sampling, the blood was replaced with an equal volume of blood from a donor dog. Blood gases were measured with an ABL Radiometer (Copenhagen Apparatus, Denmark Radiometer Inst. BMS-MK2) and hemoglobin was measured photometrically as cyanometemoglobin.
Fig. 2. Effects of intracoronary infused catecholamines or electrical nerve stimulation (ENST) on mean coronary blood pressure (mCBP) and coronary blood flow (CBF).

2a (left): mCBP during basal condition (basal) vs. mCBP following i.c. infused catecholamines or ENST (2b, right). Open circle and closed circle in the left hand panel represent the mCBP following i.c. infused adrenaline and noradrenaline, respectively.

2c (bottom): CBF during basal condition (basal) vs. CBF following i.c. infused catecholamine or ENST.

tate was measured by standard enzymatic method. Myocardial oxygen consumption (MVO$_2$) was calculated as CBF times arterio-

coronary sinus blood O$_2$ difference.

Myocardial biopsy was performed in 30 dogs to measure the creatine phosphate (CP) and
Fig. 3. Effects of intracoronary infused noradrenaline, adrenaline or electrical nerve stimulation (ENST) on coronary vascular resistance.

Fig. 4. Changes in the relationship between coronary blood flow (CBF) and myocardial oxygen consumption (MVO$_2$). The top panel shows the MVO$_2$ plotted against CBF before catecholamine activation. The middle panel shows the change in MVO$_2$ ($\Delta$MVO$_2$) realized when catecholamine was infused intracoronary, and the bottom panel shows the change in MVO$_2$ ($\Delta$MVO$_2$) resulting from electrical nerve stimulation (ENST).
lactate content in both the subendocardial and subepicardial layers in the center of the perfusion area, which was divided by using a Wollenberger Clamp, at the end of the protocol. CP was measured by Bergmeyer's method. Finally, in 11 dogs, time course of the response of Max dp/dt of the left ventricle, LVEDP and HR to electrical stimulation of stellate ganglion was observed. At the end of experiment, left ventricular tissue was weighed to standardize the CBF and MVO₂.

Experimental protocol
The dogs were allowed to stabilize for 20 min after completion of the surgical procedures. All dogs were challenged within 15 sec of coronary arterial occlusion to examine their reactivity. Dogs with a peak reactive hyperemia of less than 200% were excluded. After measuring all parameter, the CBF was gradually reduced by constricting the extracorporeal loop of the coronary cannula with a screw-clamp device to the desired CBF level. In this model, both the systemic and coronary circulation were stabilized during 30 min as previously reported. The preparation was allowed to stabilize for 5 min, and then all parameters were again measured. Thereafter, dogs were divided into 2 major groups. Group A (n = 47); these animals experienced intracoronary infusion of 0.4 µg/kg/min of noradrenaline (n = 23) or 0.2 µg/kg/min of adrenaline (n = 24). These doses were determined to be physiological from the results obtained in a previous clinical study. Noradrenaline or adrenaline was dissolved in normal saline solution so that a continuous

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intracoronary infusion was performed at a 1.0 ml/min for 5 min. Group B (n = 31); in these animals, the anterior ansa in the left stellate ganglion was stimulated at 4 Hz, 2 msec duration, 10V. This electrical nerve stimulation (ENST) was performed for 5 min. The intensity of stimulation was chosen because it produces approximately a 50% increase of Max dp/dt of the left ventricle in the normal heart, which was similar to those induced by the intracoronary administered noradrenaline or adrenaline.\(^{15}\)

**Statistics**

The results are expressed as mean standard error of the mean. Student's t test was used to evaluate the statistical significance of the hemodynamic and metabolic data.

CBF were analyzed with respect to other parameters by linear regression analysis. The Biomedical computer Programs-5R (UCLA) system was used for regression analysis. Time response data to ENST were analyzed by paired t test.

**RESULTS**

1. The effects of intracoronary infused catecholamine and ENST on systemic hemo-
dynamics, coronary perfusion pressure, CBF and coronary vascular resistance.

In this model, intracoronary infused catecholamine or ENST slightly increased the blood pressure or the heart rate but the change did not reach statistical significance. The effects of intracoronary infused catecholamine and ENST on the coronary circulation are shown in Fig. 2. In this model, coronary perfusion pressure did not significantly change following i.c. catecholamine or ENST (Fig. 2a, 2b). I.C. infused catecholamine, especially noradrenaline and ENST did, however, slightly increase CBF (Fig. 2c). This increase in CBF was mainly the result of a decrease in coronary vascular resistance (Fig. 3).

2. The critical level of CBF

Figure 4 shows the correlation between CBF and myocardial oxygen consumption (MVO₂). In the control condition, as presented in the top panel, MVO₂ was proportional to CBF (y = 0.95x + 1.20, r = 10.8). Both CA infusion and ENST increased the MVO₂ even when CBF was less than 30 ml/min/100g, and the increase of MVO₂ with both group A and B was correlated with basal CBF (Fig. 4 middle and lower panels).

The top panel of Fig. 5 shows that the arterio-coronary sinus difference for lactate was almost constant at 1.3 ± 0.4 mM when the CBF was kept over 40 ml/min/100g. Only 6 hearts with CBF of less than 40 ml/min/100g in lactate pro-
Fig. 8. Myocardial content of creatine phosphate (CP: upper panel) and lactate (lower panel) following i.c. infusion of catecholamine and electrical nerve stimulation (ENST). On the left are the values for the endocardium (Endo) and on the right are those for the epicardium (Epi).

- CBF < 30: Coronary blood flow less than 30 ml/min/100 g.
- CBF 30–50: CBF values between 30 and 50 ml/min/100 g.
- CBF 50+: CBF values over 50 ml/min/100 g.

production (minus values in Fig. 5) were shown in the basal condition.

The middle and lower panels of Fig. 5 indicate that in both group A and group B, lactate production was clearly accentuated by catecholamine in the animals with CBF below 40 ml/min/100 g. None of the hearts with CBF over 50 ml/min/100 g showed an augmented lactate production, and half of the cases with CBF between 30 and 50 ml/min/100 g had the augmented lactate production following i.c. infusion of catecholamine and ENST (Fig. 5 lower panels).

LVEDP in the control condition was not related to CBF. On the other hand, in the both group A and B catecholamine activation markedly elevated LVEDP when the CBF was less than 40
ml/min/100g (Fig. 6). Max dP/dt of left ventricle was roughly correlated with CBF (Y = 11.2X + 1154, Y; Max dP/dt, X; CBF, t = 2.38, p < 0.05) in the control condition, and both CA infusion and ENST increased Max dP/dt when CBF was over 50 ml/min/100g, but when CBF was less than 50 ml/min/100g, Max dP/dt was not observed as having a significant change in both group A and B.

The top panel of Fig. 7 shows that the ECG-ST segment was negative in almost all cases due to open chest heart (−1.2 ± 0.4 mm when CBF was over 50 ml/min/100g, −2.0 ± 0.6 mm when CBF was under 50 ml/min/100g) and was roughly correlated with CBF in the control condition (y = 0.025x −2.776, t = 2.32). The lower 2 panels of Fig. 7 reveal that catecholamine exposure in both group A and B caused ECG-ST segment elevation in 50% cases when the CBF was below 30 ml/min/100g. When the CBF was between 30 and 50 ml/min/100g, the severe ST depression was observed.

Figure 8 shows the myocardial content of CP and of lactate. In the normal perfused heart, CP content was 30.7 ± 2.9, 30.8 ± 2.7 μmoles/g.d.w., and lactate was 10.2 ± 1.2, 9.2 ± 1.0 μmoles/g.d.w., in the endocardium and epicardium, respectively.

CP depletion and lactate accumulation were clearly seen when the CBF was below 30 ml/min/100g. When the CBF was between 30 and 50 ml/min/100g/半的 samples showed reduced CP and elevated lactate, while the other half of the samples yielded normal values. In this study, there was no difference in CP and lactate content between the endocardium and epicardium when

**Fig. 9.** Time course of the response to electrical nerve stimulation (ENST) of the left anterior ansa of stellate ganglion at 4 Hz, 2 msec, 10V for 5 min. The data represent the average values from 11 dogs. Bars indicate the standard errors of the mean.

HR = heart rate; Max dP/dt = Max dP/dt of the left ventricle; LVEDP = left ventricular end-diastolic pressure.
CBF was under 50 ml/min/100g (Fig. 8).

Figure 9 shows the time course of ENST on HR, dp/dt, and LVEDP. The time course of the effects of ENST on cardiac function was examined in 11 animals. Fig. 9 shows that HR, dp/dt, and LVEDP were not significantly changed by coronary constriction only. On the other hand, ENST augmented dp/dt for the first 2 min. However, after 5 min of stimulation, dp/dt was decreased and LVEDP had increased. CBF showed no significant change in 11 dogs during 5 min of ENST, but in 3 of 11 dogs, CBF was slightly decreased following the increase of LVEDP. HR did not change at any time during ENST.

DISCUSSION

This study demonstrated that exogenous catecholamine always accentuates myocardial ischemia associated with mechanical dysfunction in the dog heart with reduced CBF below 30 ml/min/100g. At perfusion rates above 50 ml/min/100g catecholamine significantly augmented cardiac metabolism and function and no ischemic change was observed. Between 30 and 50 ml/min/100g the data were mixed. These data indicated that a critical perfusion is achieved somewhere between 30 to 50 ml/min/100g above which sympathetic stimulation is beneficial to the heart and below which sympathetic stimulation exacerbates ischemia.

This study also showed that intracoronary infused catecholamine and ENST decreases coronary vascular resistance and increases CBF independently of coronary perfusion pressure. These results on the coronary vasodilator action of the catecholamine are compatible with those reported by Hirche, Lewis et al. and Smith et al. in spite of different experimental conditions and animals.

In the present study, the anterior ansa of left stellate ganglion was stimulated to augment cardiac sympathetic nerve activity, because the anterior ansa is thought to be a quite pure cardiac sympathetic nerve and its stimulation will increase cardiac contractility without any accompanying change in heart and blood pressure. Another advantage is the distribution of its fibers mainly over the region perfused by the left coronary artery. The intensity of electrical stimulation to anterior ansa was 4 Hz, 2 msec duration, 10V.

In our previous study, using open chest dogs, it was found that ENST resulted in a rapid increase of the noradrenaline content in the coronary sinus blood which was maintained for 5 min. Both Yamaguchi et al. and Levy and Battberg reported that a maximal cardiac response was realized with an electrical stimulation of 10 Hz, 10V and 2 msec. Thus, 4 Hz of stimulation can produce a steady state condition for 5 min or longer.

The doses of noradrenaline and adrenaline were derived from clinical studies performed in our laboratory. Both endogenous and exogenous sympathetic nerve stimulation produced a 50 percent increment of dp/dt in open chest dog hearts. In this study, with moderate to severe coronary stenosis, ENST could increase dp/dt for 2 min (Fig. 9), but after that cardiac dysfunction appeared. These results indicate that activation of the sympathetic nerves can augment cardiac function, even if the heart has severe coronary stenosis, but extremely short period. In the presence of coronary stenosis, β-adrenoceptor stimulation decreased the endo/epi ratio of regional myocardial blood flow in the ischemic area, and increased myocardial ischemic injury. On the other hand, α-adrenoceptor-mediated coronary vasconstriction may play a lesser role in CBF regulation in which the vasodilatory reserve has been exhausted by the presence of coronary stenosis. Feigl et al. postulated that α-adrenoceptor stimulation has a beneficial effect by lessening transmural steal. In the dog heart with severe coronary constriction, endogenous and exogenous catecholamines may at first increase the cardiac contractility and metabolism and then decrease the endo/epi ratio of CBF via mainly the β-adrenoceptor. Elevated LVEDP brings about the increase of CVR, which finally enters the vicious circle of a more severe ischemia. About 85 percent of the dog heart is perfused from the left coronary artery, and almost all the coronary sinus blood comes from that coronary artery. In our experiments, using the Griggs-type cannula in the left main coronary artery, the CBF was between 80 and 100 ml/min/100g in the absence of stenosis. Therefore the critical CBF level, that is 30–50 ml/min/100g, should be around 40–50 percent of the resting blood flow rate.

Lekven et al. reported that intra-coronary infusion of 0.2–0.4 μg/min of isoproteorenol caused myocardial damage, when CBF was reduced to 30 percent of normal. Recently, Heusch and Deusen reported that near maximal
cardiac sympathetic stimulation for 90 seconds augmented cardiac metabolism when the circumflex coronary artery had intermediate stenosis, and produced myocardial ischemia when the coronary artery had a stenosis severe enough to abolish reactive hyperemia. These results are consistent with our present study. Namely, the activation of sympathetic activity induced myocardial ischemia in the heart with CBF reduced to 40 percent or less of normal. In those hearts, reactive hyperemia was virtually absent? Gerling et al 26 and Uchida and Murao 27 also reported that noradrenaline or ENST produced myocardial ischemia when the CBF was reduced. In the present study, we did not measure the size of the stenosis in the intravascular lumen. Gould et al 28, 29 demonstrated anatomically critical stenosis of the coronary artery. In their results, resting coronary blood flow was unaffected until the stenosis created 80 to 90 percent reduction in diameter. Beyond 80–90 percent reduction, resting CBF was reduced in parallel with the percent reduction in diameter. Elizenga and Skinner 30 found that only a 75 percent reduction in diameter reduced resting CBF and abolished reactive hyperemia. Recently, Marcus et al 31, 32 recommended measuring CBF rather than percent stenosis in order to evaluate the physiological severity of a coronary lesion. Our data would support this view since flow seemed to predict accurately the vulnerability to sympathetic nerve stimulation. In the present study a critical CBF existed between 30 to 50 ml/min/100g.

Extrapolation from the results obtained in this animal study to the patients with coronary artery stenosis should be done with caution. We would, however, predict that patients might experience very different effects, either beneficial or deleterious, with catecholamine, depending on their coronary blood flow level.

Whether the patient would benefit or suffer from sympathetic nerve stimulation would probably be impossible to predict from examination of the coronary anatomy but might be determined by measurement of blood flow in the ischemic zone.

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