744 Coronary Flow and Ventricular Function Interaction

Tuesday, March 21, 1995, 10:30 a.m.–Noon
Ernest N. Morial Convention Center, Room 61

10:30

744-1 Endogenous Nitric Oxide Attenuates Myocardial Inotropic Responses in Ischemic Myocardium of the Canine Heart

Koichi Node, Masafumi Kitakaze, Kazuo Komamura, Hiroaki Kosaka [1], Yuji Okuyama, Hiroharu Funaya, Michihiko Tada, Michitoshi Inoue, Masatsugu Hori, Takenobu Kamada. *The First Dept. of Med., Osaka Univ., Osaka, Japan;* [1] *The Dept. of Physiol I, Osaka Univ., Osaka, Japan*

Nitric oxide (NO) is reported to attenuate myocardial contraction, raising the possibility that endogenous NO decreases the inotropic response of ischemic myocardium. In 42 dogs, the left anterior descending coronary artery was perfused with blood from the left carotid artery. During reduction of perfusion pressure (103 ± 6 to 53 ± 4 mmHg) so that coronary blood flow (CBF) decreases to 60% of the control, fractional shortening (FS) of the perfused area decreased from 23.3 ± 3.3 to 8.4 ± 1.3%. Intravenous infusions of isoproterenol (ISO, 75 and 150 ng/kg/min) increased FS to 15.9 ± 3.3 and 22.5 ± 2.5%, respectively. An infusion of L-NAME, an inhibitor of NO synthase, did not alter FS in the non-ischemic condition (24.5 ± 2.1%). However, changes in FS due to reduction of CBF to 60% (FS:14.3 ± 1.3%), and intravenous infusions of ISO during coronary hypoperfusion (FS:23.3 ± 3.3 and 32.3 ± 2.8%) were augmented in the L-NAME group compared with the untreated group. Lactate extraction ratio (−4.1 ± 2.2 vs −15.6 ± 4.2%), and pH in the coronary venous blood (7.32 ± 0.03 vs 7.27 ± 0.03) in the L-NAME group were lower than the untreated group during coronary hypoperfusion. Furthermore, L-arginine restored metabolic dysfunction due to L-NAME in the ischemic myocardium. These results indicate that endogenous NO attenuates myocardial contractile function in the ischemic heart and improves myocardial metabolic function. NO and NO donors such as nitrates in the ischemic heart disease may play an important role for myocardial energy-sparing effect as well as coronary vasodilation.

10:45

744-2 Effects of Intracoronary Bradykinin on the LV Pressure-Volume Relation and Coronary Blood Flow in Anesthetized Dogs

John G. Kingma Jr., Denis Simard, Jacques R. Rouleau. *Laval University, Quebec, Canada*

Myocardial bradykinin (BK) levels increase during ischemia. BK modulates cardiac efferent nerves and affects cardiovascular hemostasis possibly via BK receptors (B_1 or B_2). We examined the effects of BK on the end-systolic LV pressure-volume relation (ESPVR; conductance catheter method) and blood flow (BF; electromagnetic flow probe) in 6 open-chest, instrumented dogs. BK (0.01–1.0 nM/kg) was injected into the circumflex artery while LV pressure-volume loops and BF were continuously monitored without and with BK B_2-receptor blockade with HOE-140 (HOE; 4.5 nM/kg; *i.v.*). At baseline before HOE, LV systolic pressure, stroke volume, end-systolic volume, the slope of the ESPVR (E_{es}), dP/dt_{max} and BF were 104 ± 10 mmHg, 14 ± 3 mL, 24 ± 4 mL, 2.9 ± 1.4 mmHg/mL, 1440 ± 62 mmHg/sec, and 33 ± 12 mL/min, respectively. With intracoronary BK, E_{es} increased in a dose-dependent manner (6.9 ± 2.4 mmHg/mL at 1.0 nM/kg, $p \leq 0.05$); BF was higher than baseline despite lower LV pressure. After HOE, LV systolic pressure increased ($p \leq 0.01$), stroke volume decreased ($p \leq 0.01$) and BF was unchanged. HOE blocked the dose-dependent BK-mediated hypotension and coronary vasodilatation but had no effect on peak reactive hyperemia following a 20 sec coronary occlusion (120 ± 47 vs 113 ± 41 mL/min; p = NS); BF repayment time decreased significantly (47 ± 4 vs 39 ± 5 sec). *Conclusions:* 1) BK augments LV contractility, 2) HOE blocks BK-mediated increases in LV contractility, and 3) HOE does not affect peak reactive hyperemia but reduces repayment time. Thus, BK lowers LV pressure and volume but increases BF secondary to augmented LV contractility. These effects may be receptor-mediated since they were significantly attenuated after BK B_2-receptor blockade.

11:00

744-3 Inhibition of Nitric Oxide Synthesis does not Increase Cardiac Contractile Response but Reduces Coronary Blood Flow Response to β-Adrenergic Stimulation in Normal Dogs

Haruo Kaneko, Takao Endo, Shinsuke Fujita, Kaname Kiuchi, Ikuyo Suzuki, Kuniya Asai, Jun Nejima, Yoshihiro Suzuki, Hirokazu Hayakawa. *Nippon Medical School, Tokyo, Japan*

Although the induction of nitric oxide (NO) synthesis has been implicated as a cause of cytokine-induced depression of cardiac β-adrenergic responsiveness, whether the NO system constitutively present in the normal myocardium plays a role in its physiologic response to β-adrenergic stimulation *in vivo* remains controversial. Accordingly, we examined the effects of low and high doses of N^W-nitro-L-arginine methyl ester (L-NAME)(10 and 100 μg/kg/min for 10 min), an NO synthase inhibitor, administered into left circumflex coronary artery (LCX) on responses of peak left ventricular (LV) dP/dt, regional wall thickening in LCX region and LCX blood flow to graded intracoronary (IC) doses of isoproterenol (ISO;0.002 to 0.016 μg/kg/min) in 7 anesthetized dogs. IC L-NAME was associated with dose-related reductions in IC acetylcholine-induced coronary vasodilation. Effects of L-NAME on ISO-induced changes are shown:

	baseline	ISO:0.002	0.004	0.008	0.016
Peak LV dP/dt (mmHg/sec) (n = 7)					
control	2029 ± 136	2586 ± 192	2820 ± 200	3309 ± 255	4120 ± 419*
low L-NAME	2171 ± 149	2566 ± 176	2894 ± 206	3214 ± 223	3707 ± 250*
high L-NAME	2114 ± 166	2326 ± 193	2560 ± 152	3014 ± 140	3354 ± 171*
Wall thickening (%) (n = 2)					
control	22 ± 7	25 ± 6	29 ± 5	33 ± 7	35 ± 9
low L-NAME	25 ± 11	25 ± 15	28 ± 19	31 ± 18	36 ± 21
high L-NAME	28 ± 17	25 ± 15	25 ± 15	31 ± 19	34 ± 15
LCX blood flow (ml/min)(n = 7)					
control	33 ± 6	48 ± 7	52 ± 6	61 ± 8	70 ± 9*
low L-NAME	36 ± 7	41 ± 8	44 ± 9	47 ± 8	52 ± 9*
high L-NAME	33 ± 7	36 ± 8	38 ± 7	40 ± 7	48 ± 8*

mean ± SEM; *p < 0.05

Thus, inhibition of NO synthesis by L-NAME did not change baseline contractility nor did it increase its response to ISO. It also did not alter baseline blood flow, but reduced significantly its response to ISO. These data strongly suggest that the NO system in the normal myocardium does not modulate contractility, but NO formation in the vasculature contributes to the β-adrenergic coronary vasodilation.

11:15

744-4 Evidence for Downward-Shift of Coronary Pressure-Flow Relationship Following a Brief Period of Ischemia in Dogs

Toshikazu Morioka [1], Masafumi Kitakaze, Tetsuo Minamino, Koichi Node, Yoshiro Shinozaki [2], Mitsuaki Chujo [2], Hidezo Mori [2], Jun Tanouchi [1], Masatsugu Hori [2], Takenobu Kamada. *The First Dept. of Med., Osaka Univ., Osaka, Japan;* [1] *Osaka Rosai Hospital Osaka, Japan;* [2] *Physiol. Dept., Tokai Univ., Isehara, Japan*

This study was undertaken to test whether a brief period of ischemia affects the coronary pressure-flow relationship during reduction of coronary perfusion pressure (CPP). The left anterior descending coronary artery was cannulated and perfused with blood from the left carotid artery in 40 open-chest dogs. Coronary blood flow (CBF) was measured during intracoronary administrations of papaverine and adenosine. Coronary pressure-flow relationship was assessed during transient reduction of CPP from 100 to 30 mmHg with 10 mmHg intervals. Coronary hyperemic flow due to adenosine and papaverine was attenuated at 30 min of reperfusion following 10 and 15 min of ischemia. In the group of transient 10 min ischemia, both fractional shortening (FS) and CBF returned to the pre-ischemic values at 30 and 60 min of reperfusion, however, marked decreases in CBF (35 ± 5 vs 56 ± 4 ml/100 g/ml at CPP = 60 mmHg, p < 0.01) during graded reductions in CPP were observed. Furthermore, both FS (6 ± 1 vs 14 ± 1% at CPP = 60 mmHg, p < 0.01) and lactate extraction ratio (−41 ± 15 vs 1 ± 6% at CPP = 60 mmHg, p < 0.05) were decreased. The endocardial vs. epicardial flow ratio was reduced relative to the control condition. The downward-shift of the coronary perfusion pressure-flow relationship and the deterioration of myocardial contractile and metabolic function during reduction of CPP were restored at 60 min of reperfusion. In contrast, in the group of transient 15 min ischemia, although both baseline FS and coronary hyperemic flow due to adenosine and papaverine remained to be at 30 and 60 min of reperfusion, the coronary perfusion pressure-flow relationship was not shifted.

Conclusion: Transient brief period of ischemia can reversibly affect the coronary pressure-flow relationship due to the reduced capability of vascular