POSTER DISCUSSION XIV

A1119

TITLE: β-ADRENERGIC RECEPTOR DESENSITIZATION DURING CARDIOPULMONARY BYPASS

AUTHORS: Schwinn DA, Leone BJ, Chesnut LC, Spahn DR, Page SO, Liggett SB
AFFILIATION: Departments of Anesthesiology and Medicine (Pulmonary), Duke University Medical Center, Durham, NC 27710

INTRODUCTION: Cardiopulmonary bypass (CPB), a process routinely employed during cardiac surgery, is one of the most potent stimulants to the release of endogenous catecholamines known (1). In the setting of CPB, elevated catecholamines may lead to β-adrenergic receptor (βAR) densensitization. Therefore, we tested the hypothesis that βAR desensitization occurs during CPB.

METHODS: Twelve dogs were anesthetized with a fentanyl/midazolam anesthetic and placed on CPB designed to mimick typical bypass occurring during cardiac surgical procedures in humans. Transmyocardial left ventricular (LV) apical samples were obtained using a 7F Tru-cut biopsy needle pre-CPB, during CPB (155 min), and 30 min post-CPB, immediately frozen in liquid nitrogen, and stored at -70°C. Myocardial membranes, prepared from biopsy specimens, were used for the following receptor studies: saturation binding (total βAR number), competition analysis (proportion of β_1AR vs β_2AR), isoproterenol-stimulated adenylyl cyclase activity (total βAR function) (2), and zinterol-stimulated adenylyl cyclase activity (isolated β_2AR function). To our knowledge, this represents the first time relatively small transmyocardial biopsies have been used for such detailed analysis of βAR subtype specific number and functional coupling.

RESULTS: βAR subtype density was stable at 112±14 fmol/mg (pre-CPB) and 103±9 fmol/mg (CPB), but decreased post-CPB to 84±7 fmol/mg. The ratio of β_1AR:β_2AR remained constant throughtout (60±3:40±3 pre-CPB, 55±3:44±3 CPB, 61±2:39±2 post-CPB) revealing that both β_1AR and β_2AR subtypes were downregulated. A different pattern was noted in the functional properties of these receptors during CPB. Decreased maximal isoproterenol stimulated adenylyl cyclase (AC) activity (252±14 to 216±12 pmol/30min/mg), submaximal isoproterenol stimulated AC activity (183±10 to 157±11 pmol/30min/mg), and zinterol stimulated AC activity (187±11 to 159±11 pmol/30min/mg) were noted during CPB, at the time when weaning from CPB takes place. However this desensitized pattern was found to be completely reversed by 30 min post-CPB.

DISCUSSION: Desensitization, a complex process reflecting both cell surface receptor number and βAR function, is composed of several distinct but inter-related processes -- receptor / G-protein uncoupling, receptor sequestration, and down-regulation (3). These data suggest that myocardial βAR desensitization does occur during CPB in healthy, non-ischemic canine myocardium and that this pattern is reversed 30 minutes after discontinuation of CPB. In addition, a slower process of βAR downregulation persists after discontinuation of CPB. Depressed myocardial function (potentially secondary to βAR desensitization) may impair a patient's ability to be weaned from CPB. Therefore, these findings may have important clinical implications for the anesthesiologist regarding management of patients during routine cardiac surgery.

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A1120

TITLE: EFFECT OF ISOFLURANE ON BAROREFLEX FUNCTION IN THE RABBIT

AUTHORS: D.J. Wilson, M.D.; L.B. Bell, Ph.D., L.M. Quandt, B.S., and J.P. Kampine, M.D., Ph.D.
AFFILIATION: Anes. Dept., Medical College of Wisconsin, and VA Medical Center, Milwaukee, WI 53295

Anesthetic management of chronically hypertensive (HT) patients presents unique clinical problems. The hemodynamic instability of these patients is presumed to be due in part to alterations in baroreflex control of efferent sympathetic activity. However, baroreflex function (i.e. mean arterial pressure (MAP) vs. renal sympathetic nerve activity (RSNA)) has not been studied directly in HT animals in the conscious or anesthetized state. Therefore, this study was designed to determine: 1) the effect of chronic hypertension on baroreflex function (i.e. MAP vs. RSNA) in the conscious and anesthetized rabbit, and 2) the effect of isoflurane (ISO) concentration on baroreflex function in normotensive and HT rabbits.

Two groups of NZW rabbits were used for this study, one HT (N=6) and one normotensive (NT; N=6). Perivascular balloon occlusion cuffs were implanted around the inferior vena cava and aorta via bilateral thoracotomies, and a renal nerve recording electrode was implanted on the left renal sympathetic nerve in all animals. RSNA is presented as percent maximum RSNA elicited by nasopharyngeal stimulation with cigarette smoke. Hypertension was induced in the HT group by fitting each kidney with a snug inert latex capsule which increased MAP 18-34 mmHg in 3.5-7.5 weeks.

On the experimental day, the central ear artery was cannulated to record arterial pressure, and the balloon catheters and recording electrodes were externalized (2% lidocaine). After placing the rabbit in a sealed plexiglass box, ventilated with room air, baroreflex curves were generated in the conscious animal by recording RSNA while altering MAP via the balloon cuffs. The animal was then anesthetized by filling the box with 4% ISO for 15 min and intubated. Baroreflex curves were again generated at the end of 15 min periods of 1.0 and 2.0 % end tidal ISO in random order. Resting MAP and RSNA for NT and HT groups are shown below.

	MAP-Control	MAP-1% ISO	MAP-2% ISO
NT	76.0±2.0	48.6±1.4	29.9±1.5
HT	102.3±19.9	75.0±19.0	51.7±18.2
	RSNA-Control	RSNA-1% ISO	RSNA-2% ISO
NT	14.9±5.4	12.9±5.5	12.3±6.8
HT	9.9±7.9	11.0±13.8	14.8±13.4

Computer generated baroreflex curves are shown in the Figure for NT and HT rabbits. Only control and 2% ISO are shown for clarity. Resting MAP and RSNA are indicated by closed circles. Baroreflex curves were shifted rightward (i.e. reset) with an increase in range in HT animals. In both groups, increasing ISO levels progressively attenuated the baroreflex. These results indicate that in awake and anesthetized animals, there is little sympathetic reserve to compensate for transient falls in MAP. In addition, HT animals produce greater changes in RSNA with transient decreases in MAP. (Supported by NIH and the VA Medical Center.)