

## A163

**TITLE:**  $\beta$ -ADRENOCEPTOR DENSITY IN DIFFERENT HUMAN HEART DISEASES AND RELATIONSHIP TO THE DEGREE OF HEART FAILURE

**AUTHORS:** M. Steinfaß, M.D., J. Lavický, Ph.D., W. Schmitz, M.D., H. Scholz, M.D.

**AFFILIATION:** Abteilung Allgemeine Pharmakologie, Universitäts-Krankenhaus Eppendorf, Universität Hamburg, Martinistraße 52 2000 Hamburg 20, FRG

Cardiac  $\beta_1$ - and  $\beta_2$ -adrenoceptors mediate positive inotropic and chronotropic effects of catecholamines<sup>1</sup>. In patients with end-stage heart failure due to idiopathic dilated cardiomyopathy (IDC) the activity of the sympathetic nervous system is increased and the total  $\beta$ -adrenoceptor density ( $B_{max}$ ) is markedly reduced<sup>2</sup>. We studied  $B_{max}$  and  $\beta_1$ - and  $\beta_2$ -adrenoceptor subtype density in relationship to the degree and etiology of heart failure.

Left ventricular biopsies (5-12 mg) were taken from prospective transplant donors serving as controls and failing human hearts (with written informed consent and approval by the Research Committee, Universität Hamburg, Hamburg, FRG).  $B_{max}$  was assessed by (-)-[<sup>125</sup>I]-iodocyanopindolol. Competition experiments with the selective  $\beta_1$ -adrenoceptor antagonist CGP 20712A (1-(2-(3-carbamoyl-4-hydroxy)phenoxyethylamino)-3-(4-(1-methyl-4-trifluoro-methyl-2-imidazolyl)phenoxy)-2-propanol methanesulfonate) were performed for calculation of  $\beta_1$ - and  $\beta_2$ -adrenoceptor subtypes.

In left ventricular biopsies from transplant donors (n=8) the  $B_{max}$  was found to be  $70.2 \pm 6.0$  fmol/mg protein (mean  $\pm$  SEM) including a  $\beta_1$ -subtype population of  $78.9 \pm 2.9$  %. In patients with moderate heart failure (NYHA II-III) due to mitral valve disease (MVD, n=5) or aortic valve disease (AVD, n=5) the  $B_{max}$  was diminished by about 18 % as compared with nonfailing controls ( $58.4 \pm 5.2$  and  $55.5 \pm 5.8$  fmol/mg protein, respectively). In patients with MVD (n=10) or AVD (n=8) and advanced heart failure (NYHA III) the  $B_{max}$  was reduced by about 38 % ( $P < 0.01$ ). A decrease in  $B_{max}$  by about 50 % ( $P < 0.01$ ) was observed in patients with these valve diseases and severe heart failure (NYHA III-IV, n=9 each). Finally, in biopsies from patients with end-stage heart failure (NYHA IV) due to MVD (n=6), AVD (n=5), IDC (n=10), or ischemic cardiomyopathy (ICM, n=7) the  $B_{max}$  was diminished by about 60 % ( $P < 0.01$ ).

On the other hand, in patients with AVD (n=27) or IDC (n=10) the  $\beta_1$ -adrenoceptor population was selectively reduced ( $P < 0.01$ ) independent of the degree of heart failure, whereas the  $\beta_2$ -adrenoceptor density remained unchanged. In patients with MVD (n=30) or ICM (n=7) both  $\beta_1$ - and  $\beta_2$ -adrenoceptors were reduced ( $P < 0.01$ ).

It is concluded that the extent of total  $\beta$ -adrenoceptor downregulation might be related to the degree of heart failure, whereas changes in  $\beta_1$ - and  $\beta_2$ -adrenoceptor subtype distribution seem to be related to the etiology of heart failure. The distinct downregulation of  $\beta$ -adrenoceptors might at least in part explain the lack of effectiveness of various positive inotropic  $\beta$ -adrenoceptor agonists in some heart diseases.

This study was supported by the DFG.

**References**

1. ISI Atlas Sci Pharmacol 1: 107 - 112, 1987
2. Circulation 82 (suppl I): I 12 - I 15, 1990

## A164

**TITLE:** ASSESSEMENT OF A NEGATIVE INOTROPIC EFFECT OF HUMAN ALBUMIN

**AUTHORS:** D. Journols MD, D. Safran MD, M. Dru MD

**AFFILIATION:** Department of Anesthesiology and Intensive Care, Hôp. Laënnec, 75007 Paris, France.

A possible negative inotropic effect of albumin has been suggested in the past using measurements of right ventricle preload conditions.<sup>1</sup> The assessment of the inotropic effects of a fluid loading solution is difficult because of the dependency of preload with cardiac performance. The aim of the present study was to evaluate the inotropic effects of albumin using the slope of the right ventricular end-systolic pressure volume relationship ( $E_{max}$ ).<sup>2</sup>

After institutional approval and informed consent, 8 patients requiring fluid loading were maintained under general anesthesia. Fluid loading was done using a G-suit in order to increase PCWP of 6 mmHg. This fluid loading was continued using 100 ml administered in 2 minutes of either 4% albumin (AL), gelatin Plasmion® (Lab Roger Bellon, GL) or saline solute (SL) in a randomized order. Then the anti-G suit was progressively deflated to maintain a constant PCWP. After each episode of fluid loading 3 hemodynamic points were achieved during apnea with 3 different preloading conditions obtained by slight suit inflation modifications (-2, 0, +2 mmHg compared to PCWP). These measurements included common hemodynamic values as cardiac output by double thermodilution, right ventricular stroke volume (Baxter 93A-754H), ionised calcium and circulating catecholamines. Telesystolic point corresponded to pulmonary sigmoide closure wave.  $E_{max}$  were assessed with 3 points in each patient after the 3 loading episodes by simple regression. Comparison between slopes and origins ( $V_0$ ) in the 3 groups were determined by ANOVA.

		Albumin	Gelatin	Saline
Ca <sup>++</sup> (mmol/l)	(n=8)	0.98 $\pm$ 0.1	0.95 $\pm$ 0.1	0.89 $\pm$ 0.2
$E_{max}$ (mmHg/ml)	(n=8)	0.14 $\pm$ 0.15 *	0.25 $\pm$ 0.1	0.28 $\pm$ 0.1
$V_0$ (ml)	(n=8)	12 $\pm$ 4 *	9 $\pm$ 2	8 $\pm$ 3
CI (L/min)	(n=24)	3.8 $\pm$ 1.1	4.2 $\pm$ 1.5	4.0 $\pm$ 1.0
HR (bpm)	(n=24)	96 $\pm$ 12	90 $\pm$ 8	101 $\pm$ 9

\* Significantly different at  $P < 0.05$

Heart rate (HR), cardiac index (CI) and systemic arterial resistances evaluation did not change.  $E_{max}$  was significantly decreased in the albumin group ( $p = 0.04$ ). A sequence effect was found implying the solute following albumin loading. This effect appeared stronger when the time lag between loading stages decreased. GL and SL are comparable and effect-free upon contractility.

These results obviously demonstrate the presence of an actual but short acting negative inotropic effect of 4% purified albumin upon human right ventricle. A sympathetic or parasympathic mediation is unlikely since HR and circulating catecholamines concentrations did not vary. Nothing can assered the reponsability of albumin for the observed effect ; other substances of this blood fraction can be involved, in particular bradykinin or activated precursors. A further comparative assessment of isolated versus ultrafiltrated albumin might answer to this question.

**References:**

1. Surgery 86:235-241, 1979
2. Circulation 77:1203-1212, 1988