Corticosteroid Effect on Down Regulation in Beta Adrenergic Receptors

Toshiyuki SAITO, Koki YAMADA, Akira KITAMURA
Korenori ISHIHARA, Haruo AMAMOTO and Ryo OGAWA

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Prolonged exposure to beta-adrenergic agonists leads to loss of hemodynamic effectiveness[1]. The mechanism of this desensitization is apparently a result of both a decrease in the number of beta-adrenergic receptors and an uncoupling of the receptors from adenyl cyclase. These changes occur with surprising rapidity. Unverferth et al., for example, demonstrated the development of tolerance to dobutamine after a 72h infusion[2]. This finding has stimulated the discussion of the relative role of inotropic support, and led to interest in the combination of classes of agents.

Lefkowitz and co-workers reported experiments that beta-adrenergic receptors are transcriptionally regulated by glucocorticoids in vitro[3]. They proved that the rate of beta-adrenergic receptor gene transcription increased 3.1 fold in the glucocorticoid treated cells.

Davies et al. reported that corticosteroid increased beta-adrenergic receptor in number in circulating polymorphonuclear leucocytes in normal human[4].

Ogawa et al. confirmed this phenomenon in the clinical situation: they adminstered methylprednisolon (MP) to postoperative hypotensive patients, and confirmed an increase in the beta-adrenoreceptor density in the circulating granulocytes, which was associated with significant improvements in the hemodynamic indexes[5]. In the present study, the authors extended the observation of Ogawa et al. directly to the myocardial receptor density and the hemodynamic state in the same situation.

Methods

Eighteen patients admitted to Nippon Medical School from May 1990 to February 1991 were subjected to this study. By consensus of the institutional physicians, patients were excluded if they showed any changes in their pre-existing clinical signs. Those patients who showed no particular changes in cardiovascular dynamics for at least a day, moreover received continuous catecholamine infusion over 72 hours were eligible. They were divided into three groups i.e. control group, dopamine administered group (DOA group) and dopamine plus dobutamine administered group (DOA-DOB group), where control group has no catecholamine treatment with the same diseases other groups have. Table 1 shows the patients' profile. There are no significant differences in age, weight or height. We administered 10 $mg \cdot kg^{-1}$ of MP

Department of Anesthesiology, Nippon Medical School, Tokyo, Japan

Address reprint requests to Dr. Saito: Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113 Japan

Table 1. Patient profile

Control Group	
3 males,	3 females
ave. age	39.3 yrs.
ave. wt.	54.9 kg
ave. ht.	164 cm
DOA Group	
4 males,	2 females
ave. age	41.7 yrs.
ave. wt.	62.3 kg
ave. ht.	159 cm
DOA-DOB Group	
3 males,	3 females
ave. age	49.6 yrs.
ave. wt.	55.2 kg
ave. ht.	162 cm

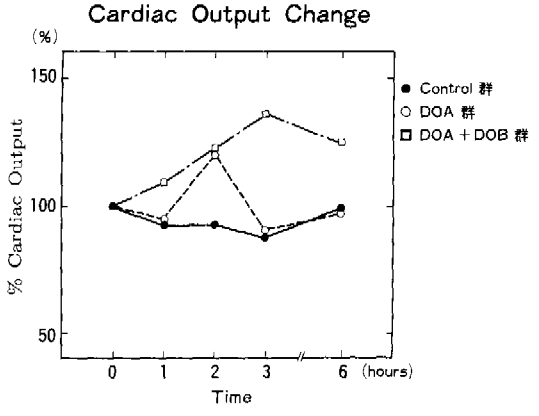

Fig. 1

intravenously to all patients. MP was purchased from Up John Co., Japan. Before, during and after the glucocorticoid administeration several hemodynamic measures were monitored.

On another six patients, we performed beta-catecholamine receptor assay in postmortem level using radioactive hydroxybenzylpindolol[6]. They are also divided into three groups i.e. control group, catecholamine administered group, and catecholamine plus methylprednisolon group. This classification was determined by the treatment when they died.

The left ventricular myocardium was removed at the necropsy period, chilled on ice, and homogenized in 11.3% (W/V) sucrose in 5 mM Tris-HCl buffer pH 7.4 containing 1 mM $MgCl_2$ with a Brinkmann Polytron homogenizer at full speed for 15 seconds. The homogenate was centrifuged at 90g for 5 min. at 4°C. The resultant supernate was centrifuged at 30,000g for 15 min. at 4°C. The final pellets enriched in plasma membranes, were resuspended in Tris-HCl buffer (50 mM Tris, 10 mM $MgCl_2$, pH 7.4) using a Brinkmann Polytron. This membrane particulate suspension was used for the binding assay.

125 I-hydroxybenzylpindolol was assayed by incubating the membrane particulate suspension (120–150 μg of protein in 0.2 ml incubation buffer) with 125 I-hydroxybenzylpindolol (0.1 ml. specific activity, 2200 Ci/mmol) for 60 min. at 37°C either in the absence or presence of 1 μM-propranolol (0.1 ml) in a final volume of 0.4 ml. The aliquot were then vacuum filtered through Gelman (Type A-E) glass fiber filter with 10 ml Tris incubation buffer. The radioactivity that remained on the filter was then counted in a gamma counter.

The means and standard deviations were calculated for each measured parameter in the hemodynamic study. Paired t tests were applied for statistical evaluation. A significant difference is indicated when P is smaller than 0.05.

Results

Figure 1 shows time course of cardiac output. The values are expressed as a percentage of that of time 0. There was a significant difference between the value at time 0 and 3 hrs after the start of infusion in the DOA-DOB group. Besides the cardiac output, we found a tendency of decrements in diastolic pressure of pulmonary artery and in systemic vascu-

Table 2. Average measured value of [125] I-hydroxybenzyl pindolol binding sites in human heart

control group	225 (fmol·mg^{-1})
catecholamine group	138
catecholamine plus steroid	217

lar resistance in this group simultaneously.

Table 2 shows measured number of beta-catecholamine receptors. Catecholamine induced down-regulation in the myocardium. Corticosteroid inhibited the down-regulation considerably.

Discussion

The tolerance of beta-adrenergic receptor to catecholamine is thought to be accomplished in 72 hrs[2]. To observe the steroid effect on the down-regulation as clearly as possible, we selected only patients who had been treated with catecholamine over 72-hour infusion. Tai-Shion Lee et al. say that MP may even be a myocardial depressant[7]. Since Corticosteroids pose several positive and negative factor on cellular function, we think that the preceeding 72-hour infusion of catecholamine is an important condition to the study of the steroid effect on the down-regulated beta-adrenergic receptors[8].

In our result MP increased the cardiac output and beta-adrenergic receptor in the myocardium. This finding concords previous reports in vitro, in vivo and in circulating granulocytes[5,8,9]. However, our result informes that the hemodynamic improvements are consequent to the increments of beta-adrenoreceptor in the myocardium.

With corticosteroid, hemodynamic condition after long term catecholamine could be improved. Further investigation is needed.

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