Augmented Vasoconstrictor Response to Head-Up Tilt in Peripheral Tissues During Beta-Receptor Blockade

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Summary. Subcutaneous and skeletal muscle blood flow in the forearm during 30° head-up tilt was studied in 15 healthy subjects before and during treatment with propranolol. Relative blood flow was estimated by the local 133Xe washout technique. Head-up tilt elicited greater vasoconstriction in both tissues during beta-receptor blockade as compared to the pretreatment period. Proximal nerve blockade with lidocaine prevented the vasoconstrictor response in subcutaneous tissue to the tilt. In skeletal muscle injection of a low dose of propranolol had no effect on the vasoconstrictor response to tilt. Therefore, the augmented vasoconstrictor response to head-up tilt during beta-receptor blockade is most probably due to centrally elicited (baroreceptor) and neurogenically mediated impulses to resistance vessels in peripheral tissues and not to "unmasking" of peripheral alpha-receptors.

Key words: propranolol, vasoconstrictor response; subcutaneous blood flow, skeletal muscle blood flow, head-up tilt, baroreceptor reflex, peripheral resistance vessels

Propranolol is a nonselective beta-blocker which affects cardiac beta-1 receptors as well as vascular and bronchial beta-2-receptors. Its acute effects are an increase in total peripheral resistance, a decrease in heart rate and cardiac output, prolonged mechanical systole and slightly decreased blood pressure in resting subjects (Port et al. 1980). The increase in total peripheral resistance has been explained by blockade of the beta-adrenergic vasodilator effect, unmasking of alpha-receptors (Opie 1980). Beta-adrenergic attenuation of alpha-adrenergic vasoconstriction has been reported both in animals and in man in pharmacological experiments during administration of adrenaline (Ross 1971; Whelan 1967). Recently, Lundvall and Gustafsson (1981) showed in cats that haemorrhage-induced sympato-adrenal activation was associated with a graded and marked beta-adrenergic inhibitory influence on vascular tone in resistance vessels of several haemodynamically important vascular regions, viz. in skeletal muscle, in the intestine and in the skin.

In man increased activity in sympathetic vasoconstrictor fibres may be elicited by application of negative pressure to the lower body or by head-up tilt. Such manoeuvres induce neurogenically mediated vasoconstriction in skeletal muscle (Beiser et al. 1970; Sundlöf and Wallin 1978), and subcutaneous tissue (Skagen and Bonde-Petersen 1982; Skagen et al. 1981). It was previously considered that only alpha-receptors were present in the skin, but more recent investigations have identified beta-receptors in skin vessels, too (Belfrage 1978; Duell 1980).

The purpose of the present study was to show whether blood flow in subcutaneous tissue and skeletal muscle was influenced by acute treatment with a non-selective beta-blocker; if there was any effect of the treatment upon the vasoconstrictor response to head-up tilt in normals, and finally to discover if any possible augmented vasoconstrictor response was elicited by a central mechanism or locally by unmasking of the alpha-receptors.

Material and Methods

Fourteen healthy males (mean age 41 years, range 31–58 years) and one female (32 years) were studied after giving their informed consent to the procedures. The subjects were investigated before and
during treatment with propranolol, the dose of which was increased gradually over a few days to reach 120 mg or a maximum of 240 mg daily. Every subject was studied within fewer than four days after starting the medication. The adequacy of the beta-blockade was demonstrated by an increase in heart rate during the repeated exercise test of less than 80% of the increase before treatment. 16 subject had any clinical signs of peripheral vascular disease, arterial hypertension, and none was taking any medicine on entry to the study. Blood flow was measured in subcutaneous tissue in nine subjects and in skeletal muscle in six subjects.

**Experimental Procedure**

Subcutaneous and skeletal muscle blood flow was estimated by the local $^{133}$Xe washout technique (Larsen et al. 1966; Lassen et al. 1964).

$^{133}$Xe in isotonic saline (0.1–0.2 ml, 3 mCi/ml) was slowly injected subcutaneously into the skin covering the brachioradial muscle, or intramuscularly in to the brachioradial muscle, respectively 60 and 20 min prior to starting the investigation. Gamma-emission from the $^{133}$Xe was detected by two NaI (TI) scintillation detectors connected to a universal printing gamma-spectrometer (Meditronic, Denmark) with a window set around the 81 KeV photo-peak of $^{133}$Xe. As the $^{133}$Xe washout follows a monoeponential course, the fractional washout constant, $k$ (min$^{-1}$), was calculated by the least squares method from the regression line of the logarithmically transformed counting rates (corrected for background activity). The perfusion coefficient, $f$, could then be calculated from the following equation (Nielsen 1972):

$$f = k \cdot \lambda \cdot 100 \text{ml/100 g/min}$$

where $\lambda$ (ml/g) is the tissue to blood partition coefficient. $\lambda$ varies with the fat content of the tissue, but remains constant in a particular tissue during any one series of measurements using the same deposition technique.

The investigations consisted of a group of three measurements on subcutaneous and skeletal muscle depots. Each measurement lasted 8–10 min, with the labelled areas kept at one of the following positions:
1) reference level, midaxillary line; 2) head-up tilt 30° with the arm at heart level (test); 3) return to reference level. The subjects were tilted slowly during continuous measurement of blood pressure and heart rate.

Relative changes in $f$ could then be calculated from the observed relative changes in $k$:

$$\frac{f_{\text{test}}}{f_{\text{ref}}} = \frac{k_{\text{test}}}{k_{\text{ref}}}$$

$f_{\text{test}}$ ist the perfusion coefficient in the test situation, and $f_{\text{ref}}$ is the average perfusion coefficient in the reference situation just before and after the test.

The effect of proximal nerve blockade (Skagen and Bonde-Petersen 1982) upon the vascular response in subcutaneous tissue to head-up tilt was studied in four of the subjects. Nerve blockade in one arm was induced by subcutaneous infiltration of lidocaine 1% in a v-shaped area 5–10 cm proximal, lateral and medial to the area under study. A further depot of $^{133}$Xe was placed subcutaneously in the contralateral arm, to serve as a control area. In a further three subjects the effect of local injection of propranolol in the brachioradial muscle was studied during head-up tilt. Propranolol 0.1 ml in isotonic saline (10 mg/l) was mixed with 0.1 ml $^{133}$Xe in isotonic saline (3 mCi/ml) and was injected into the muscle 20 min before starting the investigation. Isotonic saline 0.1 ml injected into the other arm together with the $^{133}$Xe served as the control. On another day the three subjects were reinvestigated by the same procedure, but using propranolol 0.1 mg/l.

Results were given as mean ± SEM. Student's $t$-test for paired samples was used as the test of significance. The level of significance chosen was 0.05.

**Results**

**Mean Arterial Blood Pressure and Heart Rate (Fig. 1)**

Before propranolol treatment mean arterial blood pressure in the two series (subcutaneous vs muscular) was 94.4 ± 3.5 and 97.7 ± 3.6 mmHg in the supine position, and 91.1 ± 3.4 and 97.2 ± 4.4 mmHg in the tilted position, respectively ($p > 0.4$ and $p > 0.5$).

During treatment with propranolol mean the arterial pressure in the two series was 89.3 ± 3 and 92.5 ± 4 mmHg in the supine and 88.2 ± 3.7 and 92.0 ± 4.1 mmHg in the tilted position, respectively ($p > 0.2$ and $p > 0.3$). The mean arterial pressure was not significantly decreased during propranolol treatment either in the supine ($p < 0.3$ and $p > 0.1$) or in the tilted position ($p > 0.3$ and $p > 0.1$).

Heart rate during head-up tilt increased in both series, from 65 ± 4 and 67 ± 4 beats/min in the supine to 71 ± 5 and 72 ± 4 beats/min in the tilted position, respectively ($p < 0.005$ and $p > 0.05$).

During beta-blockade, the heart rate in the two series was 56 ± 4 beats/min and 53 ± 3 beats/min in the supine and 60 ± 5 beats/min and 54 ± 2 beats/min in the tilted position, respectively ($p < 0.05$ and $p > 0.1$). The heart rate was significantly lower during propranolol treatment, both in the supine ($p < 0.02$ and $p < 0.005$) and in the tilted position ($p < 0.02$ and $p < 0.005$).