BETA-ADRENOCEPTOR BLOCKADE AND CARDIOVASCULAR RESPONSE TO THE COLD PRESSOR TEST

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Summary : Seven healthy subjects immersed a hand in random order in either warm water or in cold water at 5°C for 2 min, after taking orally a single dose of 120 *mg* of propranolol or a placebo in a double blind fashion. The cold stress resulted in a significant increase in blood pressure and the rate pressure product without a change in heart rate. Beta-adrenoceptor blockade did not affect the pressor response the cold. The changes induced by the cold stress in the cardiovascular variables in the placebo and propranolol experiments were not statistically different. The highest rate pressure product during the cold pressor test was about 109 units. This was well below the pain threshold value of about 200 found during exercise in patients with ischaemic heart disease. In the recovery phase, the cardiovascular variables reverted to pre-immersion values within 1 min inspite of continued low hand skin temperature.

Key words : beta-adrenergic blockade, cold pressor test, sympathetic reflex, rate pressure product

INTRODUCTION

Immersion of the hand in water at 4-5°C for two min invokes a sympathetically medicated cardiovascular reaction (5, 16). This procedure has been used to raise blood pressure in patients with hypertension (1), hyperkinetic heart syndrome (7), orthostatic hypotension (11) and ischaemic heart disease (22). It has also been helpful in the evaluation of cosmonaut candidates (3), studying cold adaptation (14) and acclimatisation to high altitude (19). Guazzi *et al.* in 1976 (8) reported that blood pressure rise during the cold pressor test was unimpaired in patients with hypertension on treatment with propranolol and concluded that this drug did not act centrally to produce its antihypertensive effect. Houben *et al.* (10) performed the cold pressor test in normal subjects who were given oral propranolol and found that the blood pressure rise was

not reduced though the heart rate increase was attenuated. None of these workers calculated the rate pressure product, an indicator of myocardial oxygen consumption (23). A rise in the rate pressure product to a threshold of around 200 units has been shown to cause pain of myocardial origin in patients with ischaemic heart disease undergoing exercise (23). The cold pressor test is likely to stress the myocardium as it is accompanied by elevations of both heart rate and blood pressure (and therefore a rise in the rate pressure product). It may be important to assess this stress in terms of the rate pressure product as the test has been used in patients of ischaemic heart disease. Recently, we have shown that airway calibre does not alter during the cold pressor test (4). We have also assessed the cardiovascular response including the rate pressure product in our subjects who performed the test with and without non-selective beta-adrenoceptor blockade.

MATERIAL AND METHODS

Seven healthy subjects (4 males, 3 females) who had normal cardiorespiratory function, were recruited for the study which was approved by the Medical School Ethical Committee. The subjects were not taking any medication at the time.

Each subject immersed the right hand in water at 5° or 33°C for 2 min in different runs performed in a random order with an interval of about 15 min in between. The experiment was repeated after 48 hours at the same time of the day, with the subjects having been given 120 *mg* of propranolol (ICI) or placebo orally in a double blind fashion 2 hours before the experiment

A single ecg land (CM_5) was displayed on to a Cardiokinetics Life Trace monitor and simultaneously recorded as ecg and tachograph traces using a Grass 7p4 EKG Tachograph preamplifier and a Grass 7C polygraph at 100 mm/min. The R waves of the ecg trace were used to count the heart rate. The blood pressure was recorded by a single observer with a Hawkesley Random Zero spygmomanometer in which the zero was adjusted to a new level with every measurement. This technique minimizes observer bias (21). The mean arterial pressure was calculated as 1/3 pulse pressure + diastolic pressure. An indirect estimate of the myocardial oxygen consumption (the rate pressure product) was calculated as the product of the heart rate (beats per min) and systolic pressure (mm Hg) divided by 100 (23) and expressed as units (U).

Deep body temperature was measured in the aural canal with controlled heating of the external ear (13) using a zero gradient external auditary canal thermometer (MRC). The temperature of the dorsum of the right hand was measured with a Comark Microprocessor thermometer.

After the subject was fitted with the sensors, a variable rest period was allowed for the stabilization of the external auditary canal thermomerer probes Then the blcod pressure, deep body temperature and hand temperature were measured until a steady-state was reached The heart rate was continuously monitored. The average of several steady-state readings for each variable was taken as the control value.

The subject immersed his hand in water at either 5 or 33°C for 2 min. The blood pressure was measured after 1 min of immersion, and at 1, 3 and 5 min in the post immersion period. Only one blood pressure measurement could be made during the immersion as the subject was occupied with other aspects of the experiment. Body temperature was recorded towards the end of the hand immersion phase and in the post-immersion phase. The heart rate was continuously recorded throughout but only the readings which coincide with the blood pressure measurements are reported. The experiment was reported with water at the alternate temperature after a rest of about 15 mins, and the whole process was repeated after 48 hours with the remaining tablet. The Student's paired t-test was used to determine the significance of the findings, with 5% as the critical p-value.

RESULTS

The baseline systolic, diastolic and mean arterial pressure after propranolol and placebo were not significantly different, but the heart rate and the rate pressure product (RPP) were significantly lower with propranolol ($P<1\%$, and 0.1%) (Table I). Beta-adrenoceptor blockade did not affect body temperature.

Effect of hand immersion in warm water : The cardiovascular variables were not affected by this control procedure with or without propranolol (Table I). The aural temperature did not change, though the head temperature increased slightly (Fig. 1).

Effect of hand immersion in cold water : With beta-adrenoceptor blockade, there was no significant change in the heart rate from the pre-immersion value. The systolic blood pressure increased significantly ($P<2\%$) during the test but was back to the pre-immersion value in the 1st min of recovery. The diastolic pressure also increased significantly ($P<1\%$), to recover by 1 min in the post immersion phase, as did the mean arterial pressure ($P<1\%$) and the RPP ($P<2\%$; Table I). Without beta-adrenoceptor blockade, the systolic diastolic and the mean arterial pressures rose significantly ($P<\%$) during the cold pressor test, but there was no change in the heart rate. The RPP increased significantly ($P<5\%$; Table I). The deep body temperature was not affected by

the cold immersion, but the skin temperature decreased in propranolol and the placebo conditions without a significant difference between the two. In the recovery phase, the skin temperature remained below pre-immersion levels (Fig. 1) even though the cardiovascular variables had recovered to baseline by 1 min (Table I).

TABLE I (a) : Cardiovascular responses (Mean and SEM) to immersion of hand in water at 33°C for 2 min in 7 subjects. The significance between propranolol (PR) and placebo (PL) is shown by : ** = $P < 1\%$, *** = $P < 0.1\%$. MAP is mean arterial pressure and RPP is the rate pressure product. Recovery variables have not been statistically compared to the pre-immersion values.

		Baseline	*Immersion*	*+1 min*	*+3 min*	*+5 min*
Heart Rate	PR	58.0	58.5	60.0	59.0	59.0
		2.9	2.1	2.6	2.7	3.7
		**	**			
	PL	73.0	72.0	72.0	70.0	70.0
		3.4	2.6	2.9	2.9	2.8
Systolic BP	PR	101.0	100.0	100.5	102.5	101.0
		2.7	2.1	3.7	3.8	3.8
	PL	104.6	103.1	109.7	104.6	109.0
		2.3	1.8	2.0	3.7	2.7
Diastolic BP	PR	69.0	68.0	68.0	72.0	69.0
		2.9	2.4	3.9	3.0	3.3
	PL	73.0	72.0	74.0	69.0	71.0
		2.0	2.1	2.2	3.3	3.4
MAP	PR	79.4	78.5	78.9	82.6	79.3
		2.8	2.3	3.7	3.0	3.2
	PL	82.5	82.9	85.9	81.4	83.6
		2.0	1.9	2.0	2.8	2.8
RPP	PR	58.4	57.9	59.9	60.4	59.8
		3.2	2.9	3.7	4.2	4.5
		***	***			
	PL	75.3	74.6	73.0	72.8	76.4
		2.7	2.5	2.4	2.5	4.3

TABLE I (b): Cardiovascular response to immersion of the hand in water at 5°C for 2 min. Mean and SEM given. Statistical comparison between baseline and immersion values only.* indicate P value between propranolol (PR) and placebo (PL), while # indicate P between baseline and immersion. */#=P<5%; **/## = P < 2%; ***/### = P < 1%, ****/#### = P < 0.1%.

		Baseline		*Immersion*	*+1 min*	*+3 min*	*+5 min*
Heart rate	PR	58.1		58.5	59.0	58.0	59.0
		2.0		3.2	2.7	2.9	2.9
		***		***			
	PL	74.1		75.7	71.0	70.0	69.0
		3.2		4.1	3.3	3.0	3.3
Systolic BP	PR	102.3	##	111.8	100.3	102.1	102.3
		3.5		3.9	3.9	4.5	4.2
	PL	105.2	###	120.7	103.0	109.0	107.0
		1.6		4.0	3.6	2.3	1.8
Diastolic BP	PR	69.0	###	80.0	67.0	68.0	68.0
		3.6		2.4	3.8	3.4	2.4
	PL	69.0	###	85.0	68.0	70.0	68.0
		1.9		3.3	1.9	2.0	3.1
MAP	PR	80.3	###	91.8	77.8	79.5	79.1
		3.5		2.6	3.7	3.6	3.0
	PL	80.9	###	95.6	80.3	82.9	82.5
		1.7		3.5	2.5	1.7	2.0
RPP	PR	59.8	##	65.3	58.3	55.7	59.8
		3.2		4.5	2.7	5.8	4.5
		****		****			
	PL	77.9	#	91.3	72.4	76.1	73.8
		3.2		6.6	2.9	3.4	3.4

During beta-adrenergic blockade, the changes in the cardiovascular variables from baseline brought about by the cold pressor test were slightly but not significantly greater than in the placebo experiments (Fig. 2).

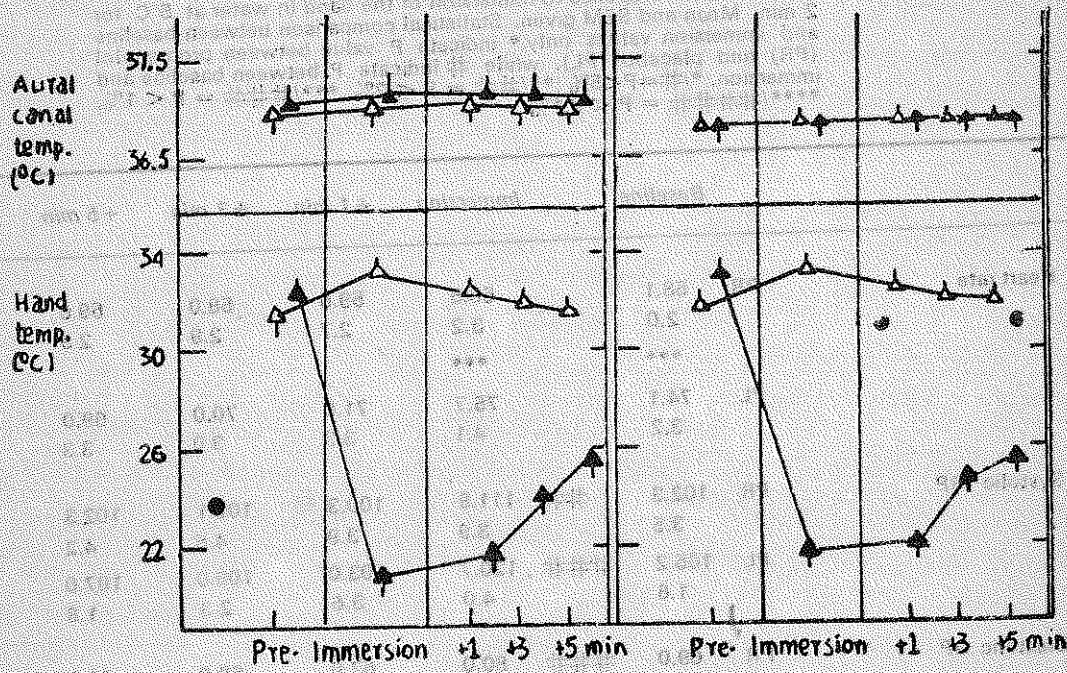

Fig. 1 : Aural canal and hand temperature (Mean and SEM) during immersion of hand in warm water (open triangles) and cold water at 5°C for 2 min (closed triangles) with propranolol (left side) and placebo (right) before, during and at 1, 3 and 5 min in the post immersion phase.

DISCUSSION

A variety of protocols have been used for the cold pressor test. Wolff (25) stated that the protocol observed did not influence the results. The "Standard cold pressor test" : immersion of the hand in water at 5°C for 2 min (2, 12, 15, 16), has been used in this study.

McDevitt (18) advocated the use of exercise heart rate reduction as a quantitative test for the effectiveness of beta-adrenoceptor blockade. A significant lowering of the resting heart rate with a single oral dose of 120 *mg* of propranolol has however been accepted as sufficient evidence for effective beta-adrenergic blockade for the present study because Pearson *et al.* (20) reported a significant reduction in the exercise heart rate of their subjects with 80 *mg* propranolol taken orally 2 hours before the experiment.

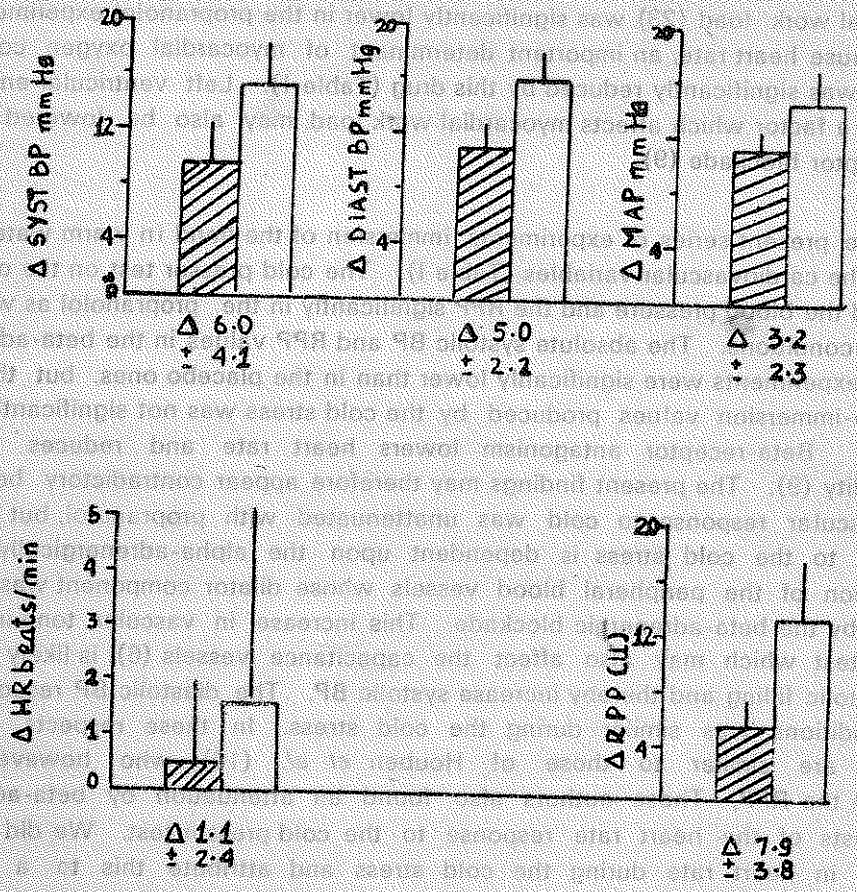

Fig. 2 : Mean changes and sem (vertical bars) from baseline values of heart rate (HR beats/min), rate pressure product (RPP), systolic blood pressure (SYST BP mm Hg), diastolic blood pressure (DIAST BP mm Hg) and mean arterial pressure (MAP mm Hg) induced by the cold pressor test with propranolol (strippled blocks) and placebo (open blocks). *delta* stands for the mean difference ± SEM between the changes in the two conditions. There were no significant differences between the mean differences.

The baseline systolic and diastolic pressure and the mean arterial pressure (MAP) after propranolol were not significantly different from measurements after the placebo. This was also found by others (17), though Houben *et al.* (10) reported a significant reduction in these variables in their subjects who had been given 240 *mg* of propranolol in divided doses over 12 hours preceeding the experiments, and not a single 120 *mg* dose as in the present study and that of Maconochie (17) who used 80 *mg*. The rate pressure product (RPP), which indicates myocardial oxygen consumption and therefore

myocardial work load (23) was significantly lower in the propranolol experiments. This was because heart rate, an important determinant of myocardial oxygen consumption (9, 23) was significantly reduced by this drug (Table I). Left ventricular end-diastolic pressure, a factor which affects myocardial work load, may also be lowered by beta-adrenoceptor blockade (9).

In the present series of experiments, immersion of the hand in warm water did not change the cardiovascular variables (Table I). The cold pressor test on the other hand increased the blood pressure and the RPP significantly in the propranolol as well as the placebo conditions. The absolute systolic BP and RPP values in the beta-adrenoceptor blocked experiments were significanly lower than in the placebo ones, but the change from pre-immersion values produced by the cold stress was not significantly different (Fig. 2). Beta-receptor antagonism lowers heart rate and reduces myocardial contractility (9). The present findings may therefore appear contradictory because the cardiovascular response to cold was unattenuated with propranolol, but the pressor response to the cold stress is dependent upon the alpha-adrenergically mediated constriction of the peripheral blood vessels whose dilator component was effectively reduced by the beta-adrenergic blockade. This increase in vascular tone in the cold pressor test which may also affect the capacitance vessels (6), is likely to increase end-diastolic filling and thereby increase systolic BP. The diastolic BP response in the two conditions was similar during the cold stress. In these respects, the present findings are similar to those of Houben *et al.* (10) who however did not calculate the RPP. These authors also found an attenuation by beta-adrenoceptor antagonists of the heart rate response to the cold pressor test. We did not see an increase in heart rate during the cold stress and attribute this to a substantial bradycardia seen in two of our subjects which offset the increase in heart rate seen in the others.

The highest value of the rate pressure product seen in the present series of experiments was about 109 U. Myocardial ischaemic pain during exercise in patients with coronary artery disease was associated with a rise in the RPP value to about 200 (23). It has been reported that the cold pressor test is not an effective stimulus for precipitating ischaemic pain in patients with angina pectoris (5, 24). The low RPP values reached in this test may be an explaination for this.

The skin temperature of the hand, which had fallen profoundly with cold immersion, had not recovered to the pre-immersion value during the recovery phase, but this did not affect the cardiovascular variables which reverted to pre-immersion levels by

1 min in the post-immersion phase (Fig. 2, Table I). This suggests that it was the pain induced by direct contact with cold water which provoked the sympathetic reflex affecting the cardiovascular system, and not the low skin temperature. Wolff (25) too had stated that it is the pain sensation rather than the cold which excites the reaction to the cold pressor test.

The finding in the present series of experiments are based on single observations on the blood pressure made in the 1st min of the cold strees. We wanted to obtain unbiased blood pressure measurements made with the Hawkesely random zero apparatus (21). This technique is more time consuming and allowed us to make only one measurement in the 1st min. Also most observers report the findings at the first minute because some degree of cold adaptation may attenuate the physiological reactions afterwards (6).

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