

EXTENDED REPORT

Oral premedication with low dose midazolam modifies the immunological stress reaction after the setting of retrobulbar anaesthesia

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Background/aims: An acute immunological stress reaction was previously reported to occur after the painful setting of retrobulbar anaesthesia before intraocular surgery. This study was conducted to find out whether an oral low dose premedication with midazolam would modify the immunological stress reaction.

Methods: 32 patients undergoing intraocular surgery using retrobulbar anaesthesia were included in a randomised, double blind trial. They received premedication with either 3.75 mg midazolam or placebo 30 minutes before the retrobulbar injection. Counts of leucocyte subpopulations, cardiovascular, and psychometric parameters were measured repetitively before and after the retrobulbar injection.

Results: The numbers of leucocytes increased significantly in the placebo group after the setting of retrobulbar anaesthesia (before retrobulbar injection: 6687 (SD 1025) cells $\times 10^6/l$; after injection: 7067 (1022) cells $\times 10^6/l$, $p=0.0009$) caused by rising numbers of neutrophils (before injection: 4111 (1063) cells $\times 10^6/l$; after injection: 4352 (1147) cells $\times 10^6/l$, $p=0.0007$) and natural killer cells (before injection: 290 (84) cell $\times 10^6/l$; after injection 354 (133) cells $\times 10^6/l$, $p=0.003$). There was no significant increase in total leucocytes (before injection: 5997 (1288) cells $\times 10^6/l$; after injection: 6189 (1215) cells $\times 10^6/l$) or in any leucocyte subpopulation in the midazolam group. A significant rise in systolic blood pressure occurred in the placebo group, but not in the midazolam group.

Conclusion: A low dose premedication with midazolam attenuates the immunological and cardiovascular stress reactions occurring with retrobulbar anaesthesia.

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The setting of retrobulbar anaesthesia is the most important single preoperative stress factor in ophthalmosurgery under regional anaesthesia, which induces a more prominent increase in plasma catecholamines than the operation itself.¹ This sympathoadrenal stress reaction results in an immediate rise in blood pressure, which may contribute to perioperative morbidity and complications, such as intraoperative "vis a tergo," a threatening prolapse of intraocular tissue.

In addition to this, we recently reported a distinct immunological stress reaction to be a further component of the sympathoadrenal stress reaction after the setting of retrobulbar anaesthesia,² as catecholamines induce a demargination of leucocytes by binding to β_2 adrenoceptors and by modifying the avidity state of adhesion molecules.³

Those study results were obtained from a randomised study which investigated the hypothesis that premedication reduces the stress reaction induced by the setting of retrobulbar anaesthesia. We now report on how far oral premedication with low dose midazolam modifies cardiovascular, psychological, and immunological parameters of this stress reaction.

Oral low dose midazolam previously proved to be a simple and effective premedication for intraocular surgery with regional anaesthesia.⁴ It combines sufficient preoperative anxiolysis, amnesia, and only moderate sedation with greatest possible safety.⁴

METHODS

Patients

A prospective, double blind, randomised, placebo controlled study was designed to include 32 female patients who were scheduled to undergo intraocular surgery using retrobulbar anaesthesia.

Female patients were included in the study if they were ASA (American Society of Anaesthesiologists) grade I or II, ranging in age from 55–85 years and weighing 45–100 kg.

Exclusion criteria were allergies to midazolam, insulin dependent diabetes mellitus, acute infections, malignant tumours, severe ischaemic heart disease (CCS (Canadian Cardiovascular Society) grade III/IV) or any neurological, haematological, or other severe organic disease.

All patients gave informed consent. The protocol for the study was approved by our regional ethics committee.

Intervention

Patients were allocated at random to one of two groups. Group I received placebo ($n=16$), group II received midazolam 3.75 mg orally (Dormicum, La Roche, Grenzach-Wyhlen, Germany; $n=16$). Premedication was given 30 minutes before the retrobulbar block.

All patients arrived at the operating section of our hospital between 7.20 am and 8.30 am in supine position. Upon arrival, all were supplied with a venous cannula. Investigations began immediately afterwards.

Blood samples for immunophenotyping were taken directly after arrival at the operating section. Thereafter, premedication was given. The next blood sample was taken after 30 minutes of resting in supine position. Retrobulbar anaesthesia was administered directly afterwards. Three further blood samples were drawn 2, 15, and 45 minutes after the procedure.

Heart rate, systolic, and diastolic blood pressure were registered simultaneously before each sampling period (In vivo 4500plus1 Puls Oxymeter, Omega 1445, In vivo Research Inc, Birmingham, AL, USA).

In addition, in order to study the anxiolytic and sedative potential of low dose midazolam, the patients' situative anxiety and their sedation were rated at four of the five sampling periods.

All examinations were carried out by the same interinvestigator.

Table 1 Rating scale of sedation intensity

Score	Rating criteria		Pre-PM	30 minutes post-PM	15 minutes post-RBB	45 minutes post-RBB
1	No sedation Patient awake	P	16	16	15	15
		M	15	12	10	14
2	Moderate sedation Patient drowsy, immediate reaction to speech	P	0	0	1	1
		M	1	3	5	2
3	Marked sedation Patient asleep, no reaction to speech but immediate reaction to tactile stimuli	P	0	0	0	0
		M	0	1	1	0
4	Strong sedation Reaction only to stronger tactile or acoustic stimuli	P	0	0	0	0
		M	0	0	0	0
5	Somnolent Difficulties in arousing the patient, immediately falling asleep again	P	0	0	0	0
		M	0	0	0	0

P = placebo, M = midazolam, PM = premedication, RBB = retrobulbar block. Figures indicate number of patients graded.

Retrobulbar anaesthesia

A mixture of 1.5 ml of a bupivacaine solution (bupivacaine 0.75% (Astra, Wedel, Germany) with the addition of 0.05 ml of naphazoline nitrate 1:30 000 (Novartis, Basle, Switzerland), 7.5 IU of hyaluronidase (Pharma Dessau, Dessau, Germany) per ml bupivacaine) and 0.5 ml of Articaine 2% (Hoechst Marion Roussel, Frankfurt, Germany) was used for the block of the eyelid according to O'Brien.⁵ For the retrobulbar injection 3.5 ml of this bupivacaine solution and 1.5 ml of Articaine 2% were injected over 30 seconds,⁶ using 35 mm, 0.5 mm blunt tipped needles. Oculopression of about 40 mm Hg was applied for 10 minutes thereafter.

Main outcome measures

Anxiety

Situative preoperative anxiety was evaluated with the Erlanger anxiety scale (EAS), a standardised German psychometric test that permits the evaluation of aspects of state anxiety.⁷ It contains 22 anxiety positive and two anxiety negative items which are to be answered by a four point rating scale. The minimum score is 24 points (minimal situative anxiety), the maximum score is 96 points (maximal situative anxiety).

Sedation

Objective signs of sedation were quantified using a rating scale derived from the Glasgow coma scale, shown in Table 1.

Pain

Two minutes after the setting of the retrobulbar anaesthesia, the subjective response to pain of injection was assessed by a self rating scale, in which "0" represented "no pain" and "10" represented "worst pain imaginable."

Leucocyte subpopulations

Leucocyte subpopulations were determined by direct immunofluorescence technique, using three colour flow cytometry. Samples of 20 µl EDTA blood were incubated with fluorescein isothiocyanate (FITC), phycoerythrin (PE), and R-phycoerythrin cyanine 5 (PE-Cy 5) conjugated monoclonal antibodies for 15 minutes at room temperature (anti-UCHT1-PE-Cy5 (CD3), anti-13B8.2-FITC (CD4), anti-B9.11-PE (CD8), anti-RMO52-PE (CD14), anti-3G8-FITC (CD16), anti-L130-FITC (CD18), anti-Immu19.2/RMO52-FITC/PE (CD45/CD14), anti-UCHL-1-PE (CD45RO), anti-B159-PE (CD56), all from Immunotech, Hamburg, Germany; anti-MEM-18-TRI (CD14), anti-CR3-PE (CD11b), anti-HL38-TRI (HLA-DR), all from Medac, Hamburg, Germany). Cells were fixed (Lysing solution, Becton-Dickinson, Heidelberg, Germany), stored at 4°C, and measured within 24 hours (FACScan flow cytometer, Becton-Dickinson).

Data acquisition and analysis were done with FACScan research software (PC-Lysis 1.0, Becton-Dickinson). Absolute cell numbers of leucocyte subsets were calculated on the basis of total leucocytes (Sysmex microcellcounter, model F-800, TOA Medical Electronics Company, Ltd, Kobe, Japan). Concentrations of haemoglobin and packed cell volume, measured simultaneously, were used to calculate a dilution factor respecting plasma volume changes referring to values before premedication.⁸

Statistics

Calculations were performed with STATISTICA software (Stat Soft, Tulsa, USA). All data are expressed as means and standard deviation (SD). Variables were tested for normal distribution with the Kolmogorov-Smirnov test. Normally distributed variables were analysed by two way analysis of variance (repeated measurement design), followed by the Scheffé post hoc comparison. The level of significance was set at a $p < 0.05$.

RESULTS

The patient characteristics are presented in Table 2. The two groups of patients did not differ significantly in age, body weight, pre-existing diseases, and surgical procedures.

Anxiety and sedation

Forty five minutes after premedication, situative anxiety was not significantly lower in the midazolam group (32.6 points) compared to the placebo group (38.5 points; $p = 0.11$ (data not shown)).

Even though midazolam led to higher sedation scores than placebo (Table 1), only one patient given midazolam showed marked sedation (grade 3; before and 15 minutes after retrobulbar anaesthesia). All patients remained cooperative and were able to follow commands given by the surgeon.

Pain

No difference between midazolam (median: 5, minimum: 2, maximum: 10) and placebo (median: 5, minimum: 0, maximum: 10) was found (data not shown).

Cardiovascular parameters

Systolic and diastolic blood pressure decreased significantly within 30 minutes after premedication in patients treated with midazolam ($p = 0.05$ and $p = 0.02$, respectively; Table 3), but not in those treated with placebo.

In the placebo group, a significant increase in systolic pressure occurred after the setting of the retrobulbar block ($p = 0.01$). This significant increase was prevented by midazolam.

Table 2 Patient characteristics

	Group 1 Midazolam (n=16)	Group 2 Placebo (n=16)
Biometric data (mean (SD))		
Age (years)	72.9 (6.9)	72.9 (7.0)
Weight (kg)	67.2 (11.6)	68.6 (12.3)
ASA grade		
I	5	4
II	11	12
Pre-existing diseases		
Diabetes mellitus (non-insulin dependent)	2	0
Arterial hypertension	2	4
Ischaemic heart disease	3	4
Cardiac insufficiency (NYHA I/II)	2	4
Arrhythmic disorders	1	2
COLD	2	1
Restrictive lung disease	1	0
Types of surgery		
Cataract surgery	12	13
Cyclo photo	1	0
Retinal surgery	3	3

Biometric data: ASA (American Society of Anesthesiologists) grade; pre-existing diseases; types of surgery. COLD = chronic obstructive lung disease; NYHA = New York Heart Association. Cyclo photo = cyclophotocoagulation. Figures indicate number of patients graded.

Total leucocyte and leucocyte subsets

Within 30 minutes after premedication, numbers of total lymphocytes, of natural killer cells (NK cells), and of CD8⁺ cells declined in both groups of patients.

In the placebo group, the setting of the retrobulbar block induced an increase in the number of leucocytes ($p=0.0008$, Table 4), which was mainly due to rising numbers of neutrophils and of natural killer cells (NK cells; $p=0.003$). Among lymphocyte subsets, there was a tendency for an increase in numbers of CD8⁺ cells, of not MHC restricted T cells, and of immature CD4⁺CD8⁺ T cells, but not in numbers of CD4⁺ cells or of B cells. Within 15 minutes after retrobulbar anaesthesia, cell numbers of NK cells and of CD8⁺ cells had returned to counts similar to those measured before retrobulbar anaesthesia (table 5).

In contrast, after the intake of midazolam, neither total leucocyte numbers nor any leucocyte subset increased significantly. Thus, 2 minutes after the block, the two study groups differed significantly in numbers of total leucocytes ($p=0.03$) and of NK cells ($p=0.002$).

Apart from this immunological stress reaction after the setting of retrobulbar anaesthesia, cell numbers of total lymphocytes and of NK cells tended to show a steady decline during the morning study period in both study groups, whereas total leucocytes and neutrophils had a tendency to increase continuously, which corresponds to well known circadian rhythms in cell numbers of leucocyte subsets.⁹

DISCUSSION

Patients for ophthalmic surgery represent a high risk group because of their age and their comorbidity. Many patients show obvious signs of emotional distress before and during the ocular procedure.

Ophthalmic surgery is most often performed under local anaesthesia. Several studies have demonstrated that peri-operative stress under general anaesthesia is associated with impaired physical, psychological, and immune function.¹⁰ However, there is also a measurable physiological and psychological stress reaction when ophthalmic surgery is carried out under regional anaesthesia. The setting of the retrobulbar anaesthesia turned out to be the most important single peri-operative stressor.¹ We hypothesised that an oral premedication with low dose midazolam would modify the psychological, physiological, and immunological stress reaction of the painful setting of retrobulbar anaesthesia.

Setting the retrobulbar block could be shown to induce a distinct immunological and cardiovascular stress reaction within the placebo group: there was a significant rise in systolic blood pressure and in the number of peripheral blood leucocytes, which was caused by the rising numbers of neutrophils and of NK cells. In addition, numbers of cytotoxic, not MHC restricted T cells, of CD8⁺ cells, and of immature CD4⁺CD8⁺ T cells had a tendency to increase. In contrast, cell numbers of CD4⁺ cells and B cells remained unchanged.

In patients who received oral low dose midazolam, the setting of retrobulbar anaesthesia induced neither a significant increase in cardiovascular parameters nor in cell numbers of total leucocytes or of any leucocyte subpopulation.

A rise in blood pressure and an increase in numbers of leucocyte subsets in peripheral blood are elements of a sympathoadrenal stress reaction. It has previously been shown that the setting of retrobulbar anaesthesia induces a doubling in plasma adrenaline, which can be modified by oral low dose midazolam.¹¹

Catecholamines may change the avidity state of adhesion molecules by binding to β_2 adrenergic receptors on subsets of circulating leucocytes.¹²⁻¹⁴ Thus, leucocytes adhering to endothelial cells will be more likely to detach from the vessel wall. This results in a shift of leucocytes from the so called "marginal pool"¹⁵ to the circulating blood.³ As midazolam decreases the stress induced release of catecholamines, fewer leucocytes are going to enter the circulating blood.

In accordance, only leucocyte subsets which have a large density of β_2 receptors, such as NK cells and CD8⁺ cells, show stress induced increases after the painful retrobulbar anaesthesia, and only their circulation patterns are affected by premedication. In contrast, CD4⁺ cells, B cells, and monocytes express fewer β_2 receptors on the cell surface.¹⁶ They therefore do not show a stress induced increase in cell numbers after the setting of the retrobulbar block, and the intake of midazolam does not alter their circulation patterns.

Table 3 Heart rates, systolic, and diastolic blood pressure (BP) (mean, SD)

		Pre-PM	30 minutes post-PM	2 minutes post-RBB	15 minutes post-RBB	45 minutes post-RBB
Systolic BP (mm Hg)	P	151.6 (24.0)	144.6 (17.3)	159.8 (24.8)**	147.2 (21.4)**	150.4 (19.2)
	M	150.3 (15.5)	140.9 (23.3)*	146.5 (21.4)	140.7 (18.2)	145.1 (23.2)
Diastolic BP (mm Hg)	P	74.7 (14.3)	75.8 (14.5)	80.1 (13.6)	74.4 (10.1)*	75.2 (13.2)
	M	80.6 (15.9)	73.9 (18.7)*	78.9 (15.5)	76.6 (9.9)	77.9 (12.7)
Heart rate (BPM)	P	73.2 (11.9)	67.2 (8.2)*	71.0 (8.9)	68.2 (8.4)	68.8 (8.5)
	M	78.4 (10.9)	74.7 (10.2)	70.8 (8.1)	70.2 (8.7)	72.1 (11.6)
	D		$p=0.03$			

BPM = beats per minute. M = midazolam. P = placebo. D = significant differences between midazolam group and placebo group. PM = premedication, RBB = retrobulbar block. Crosses denote significant differences within one group, compared to the previous blood sample (* $p<0.05$; ** $p<0.01$).

Table 4 Total leucocytes and leucocyte subpopulations (mean, SD)

Subpopulation (cells $\times 10^6/l$)		Pre PM	30 minutes post-PM	2 minutes post-RBB	15 minutes post-RBB	45 minutes post-RBB
Leucocytes	P	6556 (1018)	6687 (1025)	7067 (1022)**	6998 (1174)	7039 (1223)
	M	6031 (1316)	5997 (1288)	6189 (1215)	6279 (1332)	6379 (1486)
	D			p=0.03		
Monocytes	P	485 (138)	496 (183)	481 (113)	480 (102)	420 (85)**
	M	430 (127)	411 (129)	425 (121)	417 (109)	415 (131)
Neutrophils	P	3782 (1005)	4111 (1063)**	4352 (1147)**	4405 (1264)*	4591 (1434)
	M	3658 (1284)	3861 (1165)	3965 (1156)	4097 (1301)*	4220 (1391)
Eosinophils	P	158 (102)	151 (91)	168 (110)	157 (107)	167 (139)
	M	116 (77)	112 (60)	113 (61)	121 (69)	102 (71)
Basophils	P	65 (26)	59 (22)	72 (40)	69 (24)	81 (66)
	M	56 (32)	60 (35)	74 (75)	58 (26)	62 (26)
Lymphocytes	P	1994 (349)	1793 (399)*	1871 (593)	1817 (390)	1728 (482)
	M	1677 (572)	1455 (512)*	1484 (481)	1495 (579)	1485 (472)
	D		p=0.05			

M = midazolam. P = placebo. D = significant differences between midazolam group and placebo group. PM = premedication, RBB = retrobulbar block. Crosses denote significant differences within one group, compared to the previous blood sample (* $p < 0.05$; ** $p < 0.01$).

In our study, oral low dose midazolam was chosen for premedication in order to minimise the patient's risk, as "standard dose" administration of benzodiazepines might predispose to respiratory depression. In accordance with previous studies,⁴ 3.75 mg midazolam fulfilled the main goals of premedication for ophthalmosurgery, as it tended to induce anxiolysis and light to moderate sedation without causing too strong sedation that would result in a drowsy uncooperative patient, rendering the surgeon's handling of the patient difficult. Even though we did not compare short term memory loss between the two study groups, oral premedication with 3.75 mg midazolam has been shown before by us and by others^{17, 18} to induce significant anterograde amnesia.

However, the amount of anxiolysis induced by 3.75 mg midazolam was limited, as it failed to reach statistical significance. Alternatively, the maximum anxiolytic effect of oral low dose midazolam might have occurred at a time point after the last measurement in our study was scheduled. We acknowledge that an intravenous premedication with low dose midazolam might have resulted in an earlier onset of the anxiolytic and sedative effect of midazolam as well as in a shorter period of action.

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To the best of our knowledge, we are the first to report on perioperative immunological stress reactions during ophthalmosurgery. Similar increases in cell numbers of certain leucocyte subsets, most notably in NK cells and in CD8⁺ cells, have been known to occur in laboratory stress models studying acute psychological stresses^{19, 20} or physical exercise.²¹

It has been shown by us recently that male and female patients differ in the situative preoperative anxiety before intraocular surgery.⁴ In order to increase the homogeneity of our patient groups, our study was restricted to women. In a strict sense, our results thus apply only to female patients, and may not be extrapolated to male patients. However, to the best of our knowledge, a sex specific difference in the immunological reaction to psychological stresses has not yet been shown.

The immunological stress reaction in those patients who did not receive midazolam is transient and might seem too

Table 5 Lymphocyte subpopulations (mean, SD)

Subpopulation (cells $\times 10^6/l$)		Pre-PM	30 minutes post-PM	2 minutes post-RBB	15 minutes post-RBB	45 minutes post-RBB
B cells	P	308 (125)	303 (146)	286 (144)	309 (141)	287 (129)
	M	292 (93)	291 (83)	299 (87)	308 (87)	305 (77)
CD4 ⁺ cells (helper/inducer T cells)	P	792 (163)	725 (199)*	725 (221)	728 (209)	694 (231)
	M	587 (200)	552 (220)	568 (215)	578 (246)	588 (253)
	D	p=0.003	p=0.03			
CD8 ⁺ cells (cytotoxic/suppressor T cells)	P	403 (223)	346 (165)*	374 (245)	344 (170)	318 (194)
	M	296 (138)	230 (103)*	240 (125)	239 (131)	236 (129)
	D		p=0.02			
CD3 ⁺ CD16/56 ⁺ cells (cytotoxic, not-MHC-restricted T cells)	P	164 (125)	140 (100)	163 (162)	144 (108)	149 (119)
	M	159 (108)	119 (82)**	128 (85)	126 (95)	130 (98)
CD4 ⁺ CD8 ⁺ cells (immature T cells)	P	35 (30)	30 (24)	33 (37)	30 (25)	31 (30)
	M	37 (36)	30 (32)*	31 (26)	30 (31)	31 (27)
CD3 ⁻ CD16/56 ⁺ cells (NK cells)	P	377 (160)	290 (84)**	354 (133)**	304 (131)*	283 (130)
	M	295 (169)	191 (96)**	203 (80)	178 (93)	191 (97)
	D		p=0.01	p=0.002	p=0.01	

M = midazolam. P = placebo. D = significant differences between midazolam group and placebo group. PM = premedication, RBB = retrobulbar block. Crosses denote significant differences within one group, compared to the previous blood sample (* $p < 0.05$; ** $p < 0.01$).

minor to have any acute impact on the patient's immune surveillance. However, it cannot be ruled out that a longer lasting impairment of immune functions might occur in patients who have to submit to painful and stressful procedures repetitively and that these patients might benefit from an anxiolytic pre-procedure medication which attenuates the immunological stress reaction.

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REFERENCES

- 1 **Adams HA**, Hessemer V, Hempelmann G, *et al*. [Endocrine stress response in cataract operations with local anaesthesia.] *Klin Monatsbl Augenheilkd* 1992;**200**:273-7.
- 2 **Heine G**, Gabriel H, Weindler J, *et al*. Painful regional anaesthesia induces an immunological stress reaction: the model of retrobulbar anaesthesia. *Eur J Anaesthesiol* 2001;**18**:505-10.
- 3 **Benschop RJ**, Oostveen FG, Heijnen CJ, *et al*. Beta 2-adrenergic stimulation causes detachment of natural killer cells from cultured endothelium. *Eur J Immunol* 1993;**23**:3242-7.
- 4 **Kiefer RT**, Weindler J, Ruprecht KW. Oral low-dose midazolam as premedication for intraocular surgery in retrobulbar anaesthesia: cardiovascular effects and relief of perioperative anxiety. *Eur J Ophthalmol* 1997;**7**:185-92.
- 5 **O'Brien HD**. Anaesthesia for cataract surgery. *Am J Ophthalmol* 1964;**57**:751-60.
- 6 **Atkinson W**. In: *Anaesthesia in Ophthalmology*. Springfield, IL: 1955:60.
- 7 **Galster JV**, Spörl G. [Development of a scale which quantifies transitory and habitually states of anxiety.] *Psycho* 1979;**5**:223-6.
- 8 **Dill DB**, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol* 1974;**37**:247-8.
- 9 **Levi FA**, Canon C, Touitou Y, *et al*. Circadian rhythms in circulating T lymphocyte subtypes and plasma testosterone, total and free cortisol in five healthy men. *Clin Exp Immunol* 1988;**71**:329-35.
- 10 **Madsbad S**, Buschard K, Siemssen O, *et al*. Changes in T-lymphocyte subsets after elective surgery. *Acta Chir Scand* 1986;**152**:81-4.
- 11 **Weindler J**, Kiefer T, Rippe A, *et al*. [Endocrine stress and anxiolysis after oral premedication with low-dose midazolam and clonidine after retrobulbar block.] *Anaesthesist* 1992:154.
- 12 **Bishopric NH**, Cohen HJ, Lefkowitz RJ. Beta adrenergic receptors in lymphocyte subpopulations. *J Allergy Clin Immunol* 1980;**65**:29-33.
- 13 **Brodde OE**, Engel G, Hoyer D, *et al*. The beta-adrenergic receptor in human lymphocytes: subclassification by the use of a new radio-ligand, (+/-)-125 iodocyanopindolol. *Life Sci* 1981;**29**:2189-98.
- 14 **Benschop RJ**, Godaert GL, Geenen R, *et al*. Relationships between cardiovascular and immunological changes in an experimental stress model. *Psychol Med* 1995;**25**:323-7.
- 15 **Athens JW**, Haab OP, Raab SO. Leukokinetic studies—IV. The total blood, circulating and marginal granulocyte pools and the granulocyte turnover rate in normal subjects. *J Clin Invest* 1961;**40**:989-1001.
- 16 **Maisel AS**, Fowler P, Rearden A, *et al*. A new method for isolation of human lymphocyte subsets reveals differential regulation of beta-adrenergic receptors by terbutaline treatment. *Clin Pharmacol Ther* 1989;**46**:429-39.
- 17 **Biro P**, Weidmann G, Pietzsch S, *et al*. [The dose-dependent effects of oral premedication with midazolam.] *Anesthesiol Intensivmed Notfallmed Schmerzther* 1997;**32**:672-7.
- 18 **Weindler J**, Lieblang G, Mohamed G, *et al*. [Perioperative follow-up of physiologic and cognitive functions after oral premedication with midazolam 3.75 mg in women for retrobulbar anesthesia.] *Ophthalmologie* 1996;**93**:59-67.
- 19 **Naliboff BD**, Benton D, Solomon GF, *et al*. Immunological changes in young and old adults during brief laboratory stress. *Psychosom Med* 1991;**53**:121-32.
- 20 **Cacioppo JT**, Malarkey WB, Kiecolt-Glaser JK, *et al*. Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation. *Psychosom Med* 1995;**57**:154-64.
- 21 **Gabriel H**, Kindermann W. The acute immune response to exercise: what does it mean? *Int J Sports Med* 1997;**18**:S28-45.



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