The influence of sex hormones on ocular blood flow in women

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ABSTRACT.

Purpose: **To investigate the influence of sex hormones on ocular haemodynamics, blood flow velocities in the ophthalmic and central retinal arteries and serum levels of sex hormones were measured in pre- and postmenopausal women.**

Methods: **Colour Doppler imaging (CDI) was used to determine the flow velocities (peak systolic velocity [PSV] and end-diastolic velocity [EDV]) and the resistive index (RI) in the ophthalmic and central retinal arteries in 22 premenopausal and 32 postmenopausal women, who had never received hormone replacement therapy. Serum levels were measured for oestradiol, free testosterone and follicle-stimulating hormone. The CDI parameters were compared between the two groups and the influence of serum levels of oestradiol and testosterone on blood flow velocities and the resistive indices were analysed.**

Results: **After correcting for age and mean arterial blood pressure, an analysis of covariance disclosed a significantly lower EDV ($p = 0.02$) and a significantly higher RI ($p = 0.01$) in the central retinal artery of postmenopausal women compared with premenopausal women. Partial correlation analysis, controlling for age, revealed significant correlations between the CDI parameters and serum levels of oestradiol and testosterone. For premenopausal women, PSV ($r = 0.58$, $p = 0.04$) and EDV ($r = 0.73$, $p = 0.006$) in the ophthalmic artery correlated positively with serum oestradiol levels. The RI in the central retinal artery decreased with increasing oestradiol levels in both groups (premenopausal $r = -0.40$, $p = 0.04$; postmenopausal $r = -0.32$, $p = 0.05$). Peak systolic velocity in the central retinal artery correlated negatively ($r = -0.49$, $p = 0.04$), whereas the RI correlated positively ($r = 0.53$, $p = 0.02$) with testosterone levels in the premenopausal group. Postmenopausal women with higher testosterone levels had lower EDV ($r = -0.53$, $p = 0.007$) in the central retinal artery and higher RI in both vessels (ophthalmic artery $r = 0.48$, $p = 0.01$; central retinal artery $r = 0.61$, $p = 0.002$).**

Conclusion: **Our data provide evidence of a relationship between serum sex hormone levels and blood flow velocities and resistive indices in retrobulbar arteries. Oestradiol appears to have beneficial effects on ocular haemodynamics, whereas testosterone may act as an antagonistic to the effects of oestrogen.**

Key words: oestradiol – testosterone – menopause – ocular blood flow – colour Doppler imaging

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Introduction

Sex hormone levels change throughout a woman's lifetime, depending on her reproductive state. Alterations in hormonal status have been linked to major changes in the cardiovascular system. Epidemiological studies have demonstrated the influence of menopause and postmenopausal hormone supplementation on the incidence of coronary artery disease in women (Gordon et al. 1978; Stampfer et al. 1991) and there is an increased awareness of sex hormones, particularly oestrogen, as vasoactive substances. Evidence exists about the presence and functionality of oestrogen receptors in vascular tissue (Mendelsohn 2000) and the positive effect of hormone supplementation on blood flow characteristics has been established in many vascular beds (Gangar et al. 1991; Pirhonen et al. 1993; Reis et al. 1994). The vasodilatory effects of oestrogens have been documented in animal and human studies, and both endothelium-independent and endothelium-dependent mechanisms have been implicated (Miller 1988; Herrington et al. 1994; Keeney et al. 1994). However, the vascular effects of testosterone are not well defined.

It has already been shown that the eye is a locus of action of sex hormones (Richardson et al. 1995; Wickham et al. 2000). The prevalences of ocular diseases such as age-related macular degeneration (Smith et al. 1997) and glaucoma (Orgul et al. 1995) are different in men and women and compromised ocular perfusion may contribute to the pathogenesis of these diseases (Sergott et al. 1994,

Ciulla et al. 1999). There are data suggesting that age and gender-related differences exist in ocular blood flow (Ravalico et al. 1996; Centofanti et al. 2000a; Harris et al. 2000). Furthermore, a number of studies have described the influence of hormonal status on ocular circulation. Centofanti et al. (2000b) reported that pulsatile ocular blood flow in women decreases after menopause, and suspension of oestrogen replacement therapy in postmenopausal women causes reduction in ocular blood flow. Other studies, using Doppler imaging, have revealed conflicting results regarding the effect of menopause and postmenopausal hormone replacement therapy on the vascular tone of orbital vessels, finding reduced vascular resistance either in the central retinal artery (Belfort et al. 1995; van Baal et al. 1999) or in the ophthalmic artery (Harris-Yitzhak et al. 2000). These data implicate the possible influence of sex hormones on ocular circulation. Therefore, studying the association of blood flow parameters with serum sex hormone levels may well enhance our understanding of their contribution to ocular haemodynamics. However, to the best of our knowledge, this relationship has not been studied previously.

In the present study, we examined the flow velocities and resistive indices in the ophthalmic and central retinal arteries using non-invasive colour Doppler imaging and measured the serum levels of sex hormones (oestradiol and testosterone) in pre- and postmenopausal women. Our objective was to determine the influence of sex hormones on ocular haemodynamics.

Material and Methods

Subjects

A total of 54 women were enrolled in the study. Informed consent was obtained from each subject after the nature of the study was explained. The design of the study was approved by the Ethical Committee of our institute. A detailed medical and ophthalmic history was recorded and all subjects completed an ophthalmologic examination. The first group included 22 premenopausal women aged 20–40 years (mean age 29 ± 7.2 years). These patients had no history of any ocular disease. All were in good health with no evidence of chronic systemic disease, and all had a history of regular menstrual cycles. None of these women were taking oral contraceptives or any chronic systemic/topical medications. All subjects were studied in the follicular phase of the menstrual cycle. The second group included 32 postmenopausal women aged 45–65 years (mean age 52.1 ± 4.1 years). Postmenopausal status was defined as amenorrhoea for longer than 1 year and the presence of follicle-stimulating hormone (FSH) greater than 20 IU/ml. No subject had received any exogenous sex steroid since the time of menopause. Exclusion criteria included diabetes mellitus, uncontrolled hypertension (blood pressure $>160/100$ mm Hg), smoking, hypercholesterolaemia (total cholesterol >200 mg/dl) and cardiovascular, pulmonary, peripheral vascular or renal disease. Blood pressure, heart rate, haemoglobin and haematocrit were measured in all subjects.

All subjects underwent blood flow velocity assessment by means of colour Doppler imaging. Colour Doppler imaging (CDI) is an ultrasound technique that combines B-scan grey-scale imaging of tissue structure with coloured representation of blood movement towards or away from the sensor based on Doppler shifted frequencies and pulsed-Doppler measurement of blood flow velocities. All retrobulbar CDI examinations were performed by an experienced radiologist. Blood flow velocity was measured by means of a colour Doppler imaging device (Logiq 700 MR, GE Medical System, Milwaukee, Wisconsin, USA) using an 8.8-MHz linear transducer. Before CDI, subjects rested for 20 min in a supine position. All examinations were carried out while the patients were in supine position and the eyes were closed. The ultrasound transducer was applied to the closed eyelids using a small amount of coupling gel, and care was taken not to apply pressure to the eye to avoid iatrogenic errors in the flow measurements. One eye per subject was randomly selected for CDI measurement. Measurements of peak systolic velocity (PSV) and end-diastolic velocity (EDV) were taken of the ophthalmic and central retinal arteries. Two or more recordings were made to obtain the best possible visual shape of curve. The ophthalmic artery was traced approximately 10–15 mm behind the globe, nasal to the optic nerve after their crossing. The central retinal artery was depicted within the anterior part of the optic nerve shadow, about 2–3 mm behind the surface of the optic disc. Peak systolic velocity refers to the highest blood velocity achieved during a systole and is calculated from the frequency of the peak in the Doppler-shifted spectral waveform. End-diastolic velocity refers to the lowest velocity occurring during a diastole and is calculated from the frequency of the trough in the waveform. Pourcelot's resistive index ([PSV – EDV]/PSV) was determined in each measurement by using the unit's own software. Previous studies have demonstrated good reproducibility for CDI measurement of the vessels evaluated in this study (Lieb et al. 1991; Schemtterer et al. 1998).

Simultaneous blood samples (10 ml) were collected for the assessment of serum sex hormone levels. The blood samples were centrifuged and the resulting serum was kept at -20° until assay. Serum oestradiol levels were evaluated using chemiluminescent immunoassay by Immulite analyser (Diagnostic Products Corp., Los Angeles, California, USA). Serum-free testosterone levels were determined by radioimmunoassay by Count-A-Count analyser (Diagnostic Products Corp., Los Angeles, California, USA). Serum FSH levels were measured by the electrochemiluminescent immunoassay by Elecsys 1010/2010 Modular Analytics E170 analyser (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

The results are expressed as mean $\pm$ standard deviation. Statistical analysis was performed using SPSS Version 10.0 (SPSS Inc., Chicago, Illinois, USA). Data distribution was analysed. If data were normally distributed, then parametric statistical tests were used; otherwise non-parametric tests were used. The differences between the two study groups in age, blood pressure, heart rate, haemoglobin, haematocrit, serum sex hormone levels and ocular blood flow parameters were determined by means of unpaired *t*-test or Mann–Whitney test. The differences in ocular blood flow parameters between the groups were also determined by means of analysis of covariance (ANCOVA),

with age and mean arterial blood pressure as covariates. The relationship between ocular blood flow parameters and age and mean arterial pressure was determined by means of the Pearson correlation or the Spearman ranked correlation coefficients. Associations between blood flow parameters and serum levels of oestradiol and testosterone were analysed by partial correlation test, controlling for age. A p-value < 0.05 was considered statistically significant.

Table 1. Subject characteristics: age, mean arterial blood pressure, heart rate, haemoglobin, haematocrit and serum hormone levels (mean ± SD).

	Premenopausal ($n = 22$)	Postmenopausal ($n = 32$)	p
Age (years)	29 ± 7.2	52.1 ± 4.1	<0.0001
Mean arterial blood pressure (mmHg)	89 ± 10	97 ± 9	0.02
Heart rate (beats/min)	76 ± 8	73 ± 9	0.09
Haemoglobin (g/dl)	12.4 ± 0.9	12.8 ± 0.9	0.1
Haematocrit (%)	38.6 ± 2.1	39.1 ± 2.2	0.5
Oestradiol (pg/ml)	96.4 ± 57	19.5 ± 14.5	<0.0001
Testosterone (pg/ml)	1.9 ± 0.7	1.6 ± 0.5	0.49
FSH (mIU/ml)	5.6 ± 4	71.3 ± 33.6	<0.0001

Results

Subject characteristics and the mean values of serum sex hormone levels are shown in Table 1. Postmenopausal women were significantly older and had higher blood pressures than premenopausal women. Serum oestradiol levels in premenopausal women were significantly higher than those in postmenopausal women ($p < 0.0001$). Serum testosterone levels did not differ between the two groups ($p = 0.49$). Serum FSH levels were found to be significantly lower in premenopausal women ($p < 0.0001$).

Peak systolic velocity in the ophthalmic artery was higher in premenopausal women as compared with postmenopausal women ($p = 0.01$; Table 2). End-diastolic velocity and resistive index (RI) in the ophthalmic artery were each similar in the two groups of women. In the central retinal artery, the premenopausal women had higher PSV ($p = 0.001$) and EDV ($p < 0.0001$) and lower RI than the postmenopausal women ($p < 0.0001$; Table 2). After applying an analysis of covariance correcting for age and mean arterial blood pressure, the observed differences between the two groups were still significant for EDV ($p = 0.02$) and RI ($p = 0.01$) values measured in the central retinal artery (Table 2).

When the entire group was analysed for a correlation between ocular blood flow parameters and age, PSV in the ophthalmic artery ($r = -0.31$, $p = 0.04$) and PSV ($r = -0.48$, $p < 0.0001$) and EDV ($r = -0.55$, $p < 0.0001$) in the central retinal artery decreased with age and the RI in the central retinal artery ($r = 0.55$, $p < 0.0001$) increased with age. No significant correlation was observed between the mean arterial blood pressure and any of the blood flow parameters (ophthalmic arterial PSV: $p = 0.65$; EDV: $p = 0.09$; RI: $p = 0.15$ and central retinal arterial PSV $p = 0.72$; EDV: $p = 0.47$; RI: $p = 0.51$).

The results of partial correlations between ocular haemodynamic parameters and serum sex hormone levels are shown in Table 3. For the group of premenopausal subjects, PSV and EDV in the ophthalmic artery correlated positively with oestradiol levels ($r = 0.58$, $p = 0.04$ and $r = 0.73$, $p = 0.006$, respectively) (Figs 1 and 2). Peak systolic velocity in the central retinal artery decreased significantly with increasing testosterone levels ($r = -0.49$, $p = 0.04$). The RI in the central retinal artery correlated negatively with oestradiol ($r = -0.40$, $p = 0.04$) and positively with testosterone levels ($r = 0.53$, $p = 0.02$) (Fig. 3).

For subjects in menopause, the RI in the ophthalmic artery increased with increasing testosterone levels ($r = 0.48$, $p = 0.01$). In the central retinal artery, EDV decreased with increasing testosterone levels ($r = -0.53$, $p = 0.007$) (Fig. 4) and RI correlated positively with testosterone ($r = 0.61$, $p = 0.002$) (Fig. 3), and negatively with oestradiol levels ($r = -0.32$, $p = 0.05$).

Discussion

In this study, we examined the influence of sex hormones on ocular blood flow parameters measured by CDI. Our data showed that blood flow velocities and resistive indices in the retrobulbar arteries are significantly influenced by oestradiol and testosterone levels. Our findings further suggest that changes in hormonal activity during menopause unfavourably affect retrobulbar vascular reactivity.

The influence of hormonal status on ocular blood flow has been suggested in previous reports. Recent studies on pulsatile ocular blood flow (POBF) have revealed gender and hormonal status related alterations in choroidal circulation. Pregnancy, a time of significant increase in circulating oestrogen and progesterone, is associated with increases in the POBF (Centofanti et al. 2002) and premenopausal women have higher rates of POBF than age-matched males and postmenopausal women (Centofanti et al. 2000a). Belfort et al. (1995), using CDI, showed that pregnant women have a higher diastolic

Table 2. Mean blood flow velocities (cm/s, mean ± SD) and resistive indexes of ophthalmic and central retinal arteries in pre- and postmenopausal women.

	Premenopausal ($n = 22$)	Postmenopausal ($n = 32$)	p*	F†	p†
Ophthalmic artery					
PSV	42.6 ± 5.8	37.8 ± 8.9	0.01	0.83	0.41
EDV	13.2 ± 2.5	12.7 ± 3.5	0.53	1.48	0.34
RI	0.70 ± 0.048	0.69 ± 0.056	0.42	0.18	0.72
Central retinal artery					
PSV	14.6 ± 2.2	11.9 ± 3.1	0.001	3.91	0.06
EDV	6.7 ± 1.0	4.8 ± 1.6	< 0.0001	4.96	0.02
RI	0.61 ± 0.037	0.68 ± 0.064	< 0.0001	6.32	0.01

PSV = peak systolic velocity; EDV = end-diastolic velocity; RI = resistive index.

* p-values of unpaired *t*-test.

† F and p-values of analysis of covariance, with age and mean arterial blood pressure as covariates.

Table 3. Partial correlations between ocular blood flow parameters and serum levels of sex hormones.

		Premenopausal ($n = 22$)		Postmenopausal ($n = 32$)	
		Oestradiol	Testosterone	Oestradiol	Testosterone
Ophthalmic artery					
PSV	r	0.58	0.18	0.15	0.07
	p	0.04	ns	ns	ns
EDV	r	0.73	0.08	0.20	− 0.14
	p	0.006	ns	ns	ns
RI	r	− 0.30	0.03	− 0.01	0.48
	p	ns	ns	ns	0.01
Central retinal artery					
PSV	r	− 0.14	− 0.49	0.09	− 0.20
	p	ns	0.04	ns	ns
EDV	r	0.06	− 0.25	0.21	− 0.53
	p	ns	ns	ns	0.007
RI	r	− 0.40	0.53	− 0.32	0.61
	p	0.04	0.02	0.05	0.002

PSV = peak systolic velocity; EDV = end-diastolic velocity; RI = resistive index.
R = partial correlation coefficient; ns = not significant ($p > 0.05$).

blood flow velocity and a lower resistive index in the central retinal artery compared to non-pregnant, premenopausal and hypo-oestrogenic menopausal women, whereas they reported no significant changes in blood flow velocities and vascular resistance in the ophthalmic artery. In contrast, another recent study employing CDI (Harris-Yitzhak et al. 2000) suggested that menopause causes haemodynamic alterations in the ophthalmic and posterior ciliary arteries, but not in the central retinal artery. In the current study, postmenopausal women had lower PSV in the ophthalmic artery, and lower PSV and EDV and higher RI in the central retinal artery compared to premenopausal women. However, ageing is also known to be associated with alterations in ocular blood flow. Previous studies have demonstrated that ageing is associated with a reduction in choroidal blood flow (Ravalico et al. 1996), and an increase in the resistive index of the ophthalmic (Harris et al. 2000), central retinal (Greenfield et al. 1995; Williamson et al. 1995; Groh et al. 1996) and posterior ciliary arteries (Greenfield et al. 1995; Harris et al. 2000). Similarly, our data clearly show that ageing is associated with lower blood flow velocities measured in both vessels and a higher RI in the central retinal artery. After eliminating the effect of ageing, the differences between the pre- and postmenopausal groups were still significant for the EDV and RI values measured in the central retinal artery, but not in the ophthalmic artery. When interpreting the results of CDI, it is important to note that velocity measurements by CDI do not provide a direct measure of blood flow, as both vessel diameter and velocity are required for this determination. Despite this limitation, a number of *in vitro* and *in vivo* comparisons have noted good correlation of volumetric blood flow with Doppler flow velocities (Hansen et al. 1983; Miles et al. 1987; Spencer et al. 1991). Further considerable evidence points to a close correlation of a high resistive index and low diastolic velocity with increased vascular resistance downstream from the point of CDI measurement. (Downing et al. 1991; Spencer et al. 1991; Adamson & Langille 1992). Consequently, our data suggest that distal vascular resistance increases in the central retinal artery in menopause and that it might be related to dysfunctional retinal circulation. Previous studies (Grunwald et al. 1993; Groh et al. 1996; Embleton et al. 2002) have shown that blood flow in the retinal vessels decreases with advancing age. To our knowledge, reports studying the effect of the hormonal state on retinal microcirculation are lacking in the literature and the subject needs to be further evaluated.

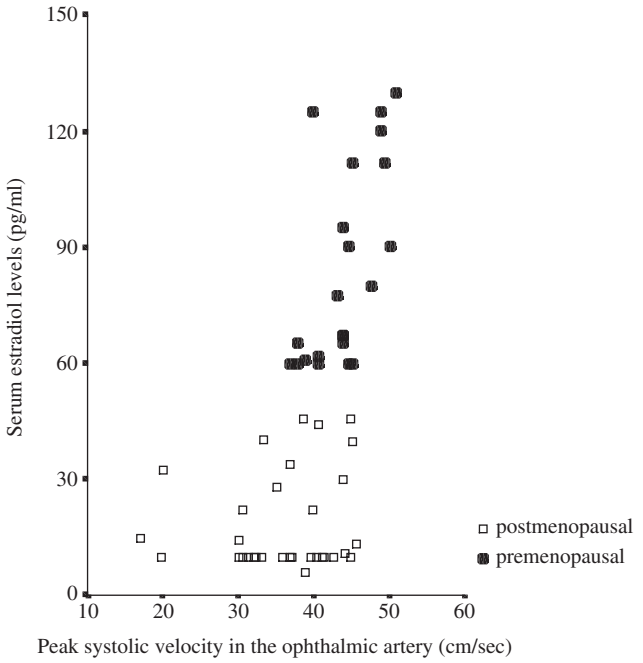

Fig. 1. Scattergram of ophthalmic arterial peak systolic velocity versus serum oestradiol levels for pre- and postmenopausal women.

It is well documented that oestrogens exert a protective effect on coronary heart disease and oestrogen replacement therapy is effective in the prevention of cardiovascular disease in postmenopausal women (Stampfer et al. 1991). Furthermore, there are data suggesting that oestrogen replacement therapy improves global cerebral perfusion (Funk et al. 1991) and reduces the pulsatility index in internal carotid and middle cerebral arteries (Penotti et al. 1993). In a prospective study conducted by Van Baal et al. (1999), the favourable effect of sequentially combined hormone replacement therapy on vascular impedance in uterine and central retinal arteries has been demonstrated. Oestrogen replacement therapy in postmenopausal

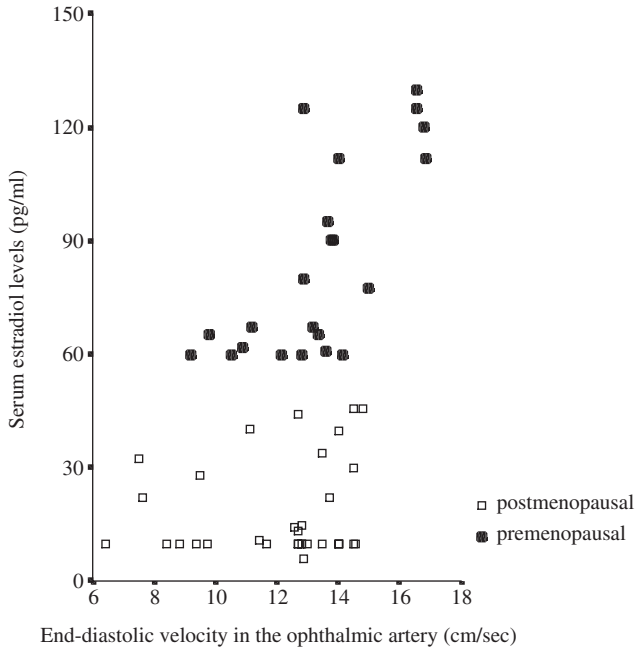

Fig. 2. Scattergram of ophthalmic arterial end-diastolic velocity versus serum oestradiol levels for pre- and postmenopausal women.

women also reduces the resistive index in the ophthalmic artery (Harris-Yitzhak et al. 2000) and the suspension of treatment induces a reduction in POBF (Centofanti et al. 2000b).

Altogether, these findings implicate an important role of sex steroids in vascular pathophysiology and further suggest the possible influence of serum levels of sex steroids on vascular dynamics. Shamma et al. (1992) studied velocity changes in the middle cerebral artery during controlled ovarian stimulation after pituitary suppression and concluded that oestrogen levels are correlated with flow velocities and pulsatility index in this vessel. However, verification of a significant correlation between sex hormone levels and ocular blood flow has not been previously demonstrated.

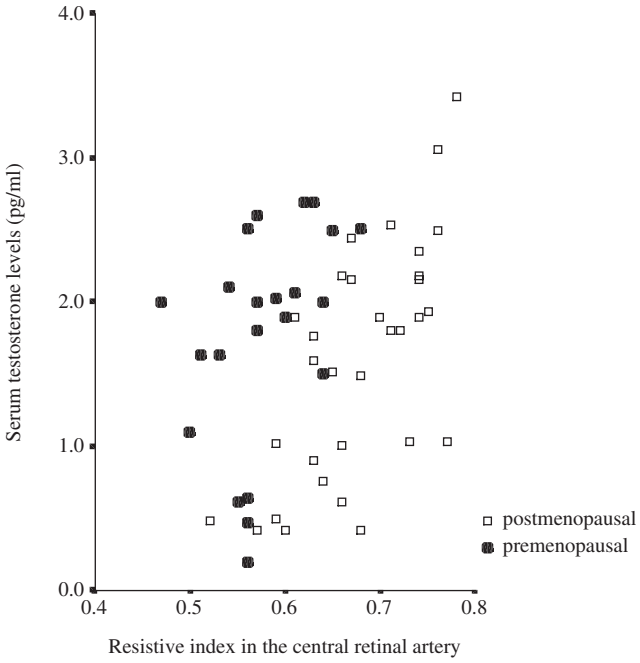

Fig. 3. Scattergram of central retinal arterial resistive index versus serum testosterone levels for pre- and postmenopausal women.

The results of this study showed that blood flow and vascular tone in retrobulbar arteries are influenced by the serum levels of oestradiol and testosterone. In premenopausal women, flow velocities in the ophthalmic artery correlated positively with oestradiol levels, which suggests that oestradiol enhances perfusion in this vessel. The combination of increased PSV with increased EDV at a constant RI is consistent with increased total blood flow through the vessel (Spencer et al. 1991). Moreover, our finding of decreased RI in the central retinal artery associated with higher oestradiol levels further suggests that oestradiol may reduce resistance to flow in the retinal circulation.

Oestrogen production by the ovaries does not continue beyond menopause and the circulating oestradiol level decreases to 10–20 pg/ml. However, oestrogen levels in postmenopausal women can be significant, principally due to the extraglandular conversion of androgens (androstenodione and testosterone) to oestrogen (Speroff et al. 1994). In the present study, although the average level of oestradiol was significantly lower (19.5 pg/ml) in postmenopausal women, oestradiol levels showed considerable variation (6.1–62.2 pg/ml). Postmenopausal women with higher serum oestradiol levels had lower RI in the central retinal artery, however, the favourable effects of oestradiol on ophthalmic artery velocities were no longer evident after menopause.

The beneficial effects of oestrogen replacement on serum lipid profile (high density lipoprotein increase and low density lipoprotein decrease) is the best known mechanism by which the protection against coronary artery disease is obtained; however, this accounts for only 25% of the overall protection (Bush et al. 1987; Gruchow et al. 1988). Animal studies have indicated that oestrogen may have vascular effects independent of changes in the lipoprotein profile and suggested oestrogen mediated improvement in endothelial function (Miller et al. 1988; Williams et al. 1992; Keeney et al. 1994). However, the exact mechanism of the endothelial effects of oestrogens are still unclear. The favourable effects of oestrogens on blood flow may result from vascular smooth muscle relaxation

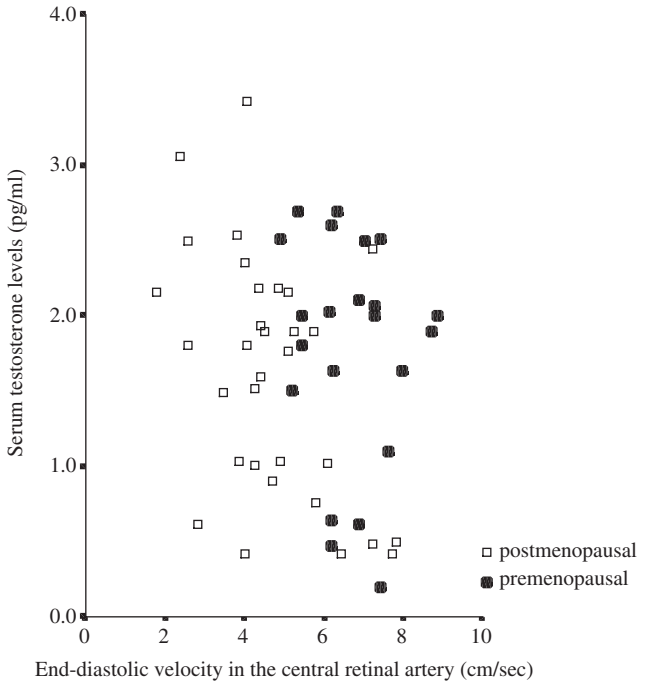

Fig. 4. Scattergram of central retinal arterial end-diastolic velocity versus serum oestradiol levels for pre- and postmenopausal women.

caused by enhanced production of endothelium-derived relaxing factors, such as nitric oxide and prostacyclin or inhibition of the release or activity of vasoconstrictor substances such as endothelin (Mikkola et al. 1998) and angiotensin II (Proudler et al. 1995). There are also data to suggest that the action of oestrogen on vascular smooth muscle is mediated in part by a calcium channel blocker effect (Salom et al. 2001). These effects are evidently mediated by oestrogen receptors in endothelial cells (Mendelsohn 2000).

The vascular effects of testosterone, however, are not well defined. Cardiovascular diseases are often considered to be predominantly a male health problem and it has been suggested that testosterone exerts deleterious effects on cardiovascular function (Lerner & Kannel 1986). Previous animal and human experiments studying the arterial effects of testosterone have shown conflicting results. Hutchison et al. (1995) found that physiological concentrations of testosterone impair endothelium-dependent vasorelaxation in cholesterol-fed rabbits. In rats, androgens mediate important sex differences in cardiovascular responses, with males showing impaired endothelium-dependent responses compared with females (Maddox et al. 1987). In contrast, however, vasodilatory effects of supraphysiological doses of testosterone have also been described in rabbits and dogs (Yue et al. 1995; Chou et al. 1996). In humans, high testosterone levels have been correlated with increased coronary risk factors in older women (Haffner et al. 1995) and deprivation of physiological levels of androgens have been associated with enhanced endothelial function in adult men (Herman et al. 1997). The cellular and molecular mechanisms underlying vascular responses to testosterone is unclear. Testosterone decreases high density lipoprotein levels in both men and women (Sacks et al. 1995) and testosterone derivatives can exert vasoconstrictor influences, including decreases in prostacyclin production (Nakao et al. 1981). It is possible that there are direct effects of androgens on the vessel wall, as steroid receptors are known to exist in the vasculature (Horwitz & Horwitz 1982).

The present study demonstrates that higher concentrations of serum testosterone are associated with decreased PSV and increased RI in the central retinal artery in premenopausal women. After menopause, with the disappearance of follicles and oestrogen, the elevated gonadotropins drive the remaining stromal tissue in the ovary to a level of increased testosterone secretion and testosterone levels do not fall appreciably (Andreyko et al. 1992). The postmenopausal ovary in most women secretes more testosterone than the premenopausal ovary and together with the marked decline in oestrogens, the androgen/oestrogen ratio increases after menopause. Our data show that the antagonistic influence of testosterone on retrobulbar circulation is more prominent after menopause, evidenced by significant positive correlations of testosterone levels with resistive indices in both vessels. Thus, adverse effects of androgens unopposed by the beneficial effects of oestrogens during the hypo-oestrogenic state may contribute to impaired blood flow velocities and increased vascular resistance in orbital vessels in postmenopausal subjects.

In summary, our data provide evidence for a relation between serum sex hormone levels and retrobulbar circulation. Oestradiol seems to have beneficial effects on ocular haemodynamics, whereas testosterone may act as an antagonistic to the favourable effects of oestrogen. We conclude that hormonal changes provoked by menopause may contribute to alterations in ocular haemodynamics.

References

Adamson S & Langille B (1992): Factors determining aortic and umbilical blood flow pulsatility in fetal sheep. Ultrasound Med Biol **18**: 255–266.

Andreyko JL, Monroe SE, Marshall LA, Fluker MR, Nerenberg CA & Jaffe RB (1992): Concordant suppression of serum immunoreactive luteinizing hormone (LH), follicle-stimulating hormone, α subunit bioactive LH and testosterone in postmenopausal women by a potent gonadotropin releasing hormone antagonist (Detirelix). J Clin Endocrinol Metab **74**: 399–405.

van Baal WM, Kenemans P, Stehouwer CDA, Peters-Muller ERA, van Vugt JMG & van der Mooren M (1999): Sequentially combined hormone replacement therapy reduces impedance to flow within the uterine and central retinal arteries in healthy postmenopausal women. Am J Obstet Gynecol **181**: 1365–1373.

Belfort MA, Saade GR, Snabes M, Dunn R, Moise KJ, Cruz A & Young R (1995): Hormonal status affects the reactivity of the cerebral vasculature. Am J Obstet Gynecol **172**: 1273–1278.

Bush TL, Barrett-Conor E, Cowan LD, Criqui MH, Wallace RB, Suchindran CM, Tyroler HA & Rifkind BM (1987): Cardiovascular mortality and non-contraceptive

oestrogen use in women: results from the Lipid Research Clinic's Programme Follow-Up Study. Circulation **75**: 1002–1012.

Centofanti M, Bonini S, Manni GL, Guinetti-Neuschüler C, Bucci MG & Harris A (2000a): Do sex and hormonal status influence choroidal circulation? Br J Ophthalmol **84**: 786–787.

Centofanti M, Migliardi R, Bonini S, Manni GL, Bucci MG, Pesavento CB, Amin CS & Harris A (2002): Pulsatile ocular blood flow during pregnancy. Eur J Ophthalmol **12**: 276–280.

Centofanti M, Zarfati D, Manni GL, Bonini S, Migliardi R, Oddone F, Harris A & Bucci MG (2000b): The influence of oestrogen on the pulsatile ocular blood flow. Acta Ophthalmol Scand **232**: 38–39.

Chou TM, Sudhir K, Hutchison SJ, Ko E, Amidon T, Collins P & Chatterjee K (1996): Testosterone induces dilatation of canine coronary conductance and resistance arteries in vivo. Circulation **94**: 2614–2619.

Ciulla TA, Harris A, Chung HS, Dannis RP, Kagemann L, McNulty L, Pratt LM & Martin BJ (1999): Colour Doppler imaging discloses reduced ocular blood flow velocities in non-exudative age-related macular degeneration. Am J Ophthalmol **128**: 75–80.

Downing G, Yarlagadda A & Maulik D (1991): Comparison of the pulsatility index and input impedance parameters in a model of altered haemodynamics. J Ultrasound Med **10**: 317–321.

Embleton SJ, Hosking SL, Roff Hilton EJ & Cunliffe IA (2002): Effect of senescence on ocular blood flow in the retina, neuroretinal rim and lamina cribrosa, using scanning laser Doppler flowmetry. Eye **16**: 156–162.

Funk JL, Mortel KF & Meyer JS (1991): Effects of oestrogen replacement therapy on cerebral perfusion and cognition among postmenopausal women. Dementia **2**: 268–272.

Gangar KF, Vyas S, Whitehead M, Crook D, Meire H & Campbell S (1991): Pulsatility index in internal carotid artery in relation to transdermal oestrodiol and time since menopause. Lancet **338**: 839–842.

Gordon T, Kannel WB, Hjortland MC & McNamara PM (1978): Menopause and coronary heart disease: the Framingham Study. Ann Int Med **89**: 157–161.

Greenfield DS, Heggerick PA & Hedges TR (1995): Colour Doppler imaging of normal orbital vasculature. Ophthalmology **102**: 1598–1605.

Groh MJM, Michelson G, Langhans M & Harazny J (1996): Influence of age on retinal and optic nerve head blood circulation. Ophthalmology **103**: 529–534.

Gruchow HW, Anderson AJ, Barboriak JJ & Sobocinski KA (1988): Postmenopausal use of oestrogen and occlusion of coronary arteries. Am Heart J **115**: 954–959.

Grunwald JE, Piltz J, Patel N, Bose S & Riva CE (1993): Effect of ageing on retinal macular microcirculation: a blue field stimulation study. Invest Ophthalmol Vis Sci **34**: 3609–3613.

Haffner SM, Newcomb PA, Marcus PM, Klein BE & Klein R (1995): Relation of sex hormones and dehydroepiandrosterone sulfate (DHEA-SO4) to cardiovascular risk factors in postmenopausal women. Am J Epidemiol **142**: 925–934.

Hansen N, Stonestreet B, Rosenkrantz T & Oh W (1983): Validity of Doppler measurements of anterior cerebral artery blood flow velocity: correlation with brain blood flow in piglets. Pediatrics **72**: 526–531.

Harris A, Harris M, Biller J, Garzozi H, Zarfty D, Ciulla TA & Martin B (2000): Ageing affects the retrobulbar circulation differently in women and men. Arch Ophthalmol **118**: 1076–1080.

Harris-Yitzhak M, Harris A, Ben-Refael Z, Zarfati D, Garzozi HJ & Martin BJ (2000): Oestrogen replacement therapy: effects on retrobulbar haemodynamics. Am J Ophthalmol **129**: 623–628.

Herman SM, Robinson JT, McCredie RJ, Adams MR, Boyer MJ & Celermajer DS (1997): Androgen deprivation is associated with enhanced endothelium-dependent dilatation in adult men. Arterioscler Thromb Vasc Biol **17**: 2004–2009.

Herrington DM, Braden GA, Williams JK & Morgan TM (1994): Endothelium-dependent coronary vasomotor responsiveness in postmenopausal women with and without oestrogen replacement therapy. Am J Cardiol **73**: 951–952.

Horwitz KB & Horwitz LD (1982): Canine vascular tissues are targets for androgens, oestrogens, progestins and glucocorticoids. J Clin Invest **69**: 750–758.

Hutchison SJ, Slevers RE, Zhu BQ, Sun YP, Sudhir K, Deedwania PC, Parmley WW & Chatterjee K (1995): Physiological concentrations of testosterone impair endothelium-dependent vasorelaxation in hypercholesterolaemic rabbits exposed to tobacco smoke. Circulation **92** (1): 168.

Keeney JF, Shwaery GT, Xu A, Nicolosi RJ, Loscalzo J, Foxall TL & Vita JA (1994): 17β-Oestradiol preserves endothelial vasodilator function and limits low density lipoprotein oxidation in hypocholesterolemic swine. Circulation **89**: 2251–2259.

Lerner DJ & Kannel WB (1986): Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham Study. Am Heart J **11**: 383–390.

Lieb WE, Cohen SM, Merton DA, Shields JA, Mitchell DG & Goldberg BB (1991): Colour Doppler imaging of the eye and the orbit: technique and normal vascular anatomy. Arch Ophthalmol **109**: 527–531.

Maddox YT, Falcon JG, Ridinger M, Cunard CM & Ramwell P (1987): Endothelium-dependent gender differences in response of the rat aorta. J Pharmacol Exp Ther **240**: 392–395.

Mendelsohn ME (2000): Non-genomic, ER-mediated activation of endothelial nitric oxide synthase: how does it work? What does it mean? Circ Res **87**: 956–960.

Mikkola T, Viinikka L & Ylikorkala O (1998): Oestrogen and postmenopausal oestrogen/progestin therapy: effect on endothelium dependent prostocyclin, nitric oxide and endothelin-1 production. Eur J Obstet Gynaecol Reprod Biol **79**: 75–82.

Miles RD, Menke JA, Boshirer M & Colliver JA (1987): Relationship of five Doppler measures with flow in an *in vitro* model and clinical findings in newborn infants. J Ultrasound Med **6**: 397–404.

Miller VM, Gisclard V & Vanhoutte PM (1988): Modulation of endothelium dependent and vascular smooth muscle responses by oestrogens. Phlebology **224**: 19–22.

Nakao J, Change WC, Murato SI & Orimo H (1981): Testosterone inhibits prostacyclin production by rat aortic smooth muscle cells in culture. Atherosclerosis **39**: 203–209.

Orgul S, Flammer J & Gasser P (1995): Female preponderance in normal tension glaucoma. Ann Ophthalmol **27**: 355–359.

Penotti M, Nencioni T, Gabrielli L, Farina M, Castiglioni E & Polvani F (1993): Blood flow variations in internal carotid and middle cerebral arteries induced by postmenopausal hormone replacement therapy. Am J Obstet Gynecol **169**: 1226–1232.

Pirhonen JP, Vuento MH, Mäkinen JI & Salmi TA (1993): Longterm effects of hormone replacement therapy on the uterus and on uterine circulation. Am J Obstet Gynecol **168**: 620–623.

Proudler AJ, Ahmed AI, Crook D, Fogelman I, Rymer JM & Stevenson JC (1995): Hormone replacement therapy and serum angiotensin-converting enzyme activity in postmenopausal women. Lancet **346**: 89–90.

Ravalico G, Toffoli G, Pastori G, Crocè M & Calderini S (1996): Age-related ocular blood flow changes. Invest Ophthalmol Vis Sci **37**: 2645–2650.

Reis SE, Gloth ST, Blumenthal RS, Resar JR, Zacur HA, Gerstenblith G & Brinker JA (1994): Ethinyl oestradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. Circulation **89**: 52–60.

Richardson PSR, Nichols C, Parsons MA & Rennie IG (1995): Sex steroid hormone receptors in the human retina and choroid: an immunocytochemical study. Invest Ophthalmol Vis Sci **36**: S128.

Sacks FM, Gerhard M & Walsh BW (1995): Sex hormones, lipoproteins and vascular reactivity. Curr Opin Lipidol **6**: 161–165.

Salom JB, Burguete MC, Perez-Asensio FJ, Torregrosa G & Albroch E (2001): Relaxant effects of 17β-oestradiol in cerebral arteries through Ca (2+) entry inhibition. J Cereb Blood Flow Met **21**: 422–429.

Schemtterer L, Dallinger S, Findl O, Streen K, Graselli U, Eichler HG & Woltz M (1998): Non-invasive investigation of the normal ocular circulation in humans. Invest Ophthalmol Vis Sci **39**: 1210–1220.

Sergott RC, Aburn NS, Trible JR, Costa VP, Lieb WE & Flaharty PM (1994): Colour Doppler imaging: methodology and preliminary results in glaucoma. Surv Ophthalmol **38** (Suppl): 65–70.

Shamma FN, Fayad P, Brass L & Sarrel P (1992): Middle cerebral artery blood velocity

during controlled ovarian hyperstimulation. Fertil Steril **52**: 1022–1025.
Smith W, Mitchell P & Wang JJ (1997): Gender, oestrogen, hormone replacement and age-related macular degeneration: results from the Blue Mountains Eye Study. Aust N Z J Ophthalmol **25** (1): 13–15.
Spencer JAD, Guissani DA, Moore PJ & Hanson MA (1991): *In vitro* validation of Doppler indices using blood and water. J Ultrasound Med **10**: 305–308.
Speroff L, Glass RH & Kase NG (1994): Menopause and postmenopausal hormone replacement therapy. In: Clinical Gynecologic Endocrinology. Baltimore: Williams & Wilkins. 583–649.
Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE & Hennekens CH (1991): Postmenopausal oestrogen therapy and cardiovascular disease: 10-year follow-up from the nurses' health study. N Engl J Med **325**: 756–762.
Wickham LA, Jianping G, Toda I, Rocha EM, Ono M & Sullivan DA (2000): Identification androgen, oestrogen and progesterone reseptor mRNAs in the eye. Acta Ophthalmol Scand **78**: 146–153.
Williams JK, Adams MR, Herrington DM & Clarkson TB (1992): Short-term administration of oestrogen and vascular responses of coronary arteries. J Am Coll Cardiol **20**: 452–457.
Williamson TH, Lowe GD & Baxter GM (1995): Influence of age, systemic blood pressure, smoking and blood viscosity on orbital blood velocities. Br J Ophthalmol **79**: 17–22.
Yue P, Chatterjee K, Beale C, Poole-Wilson P & Collins P (1995): Testosterone relaxes rabbit coronary arteries and aorta. Circulation **91**: 1154–1160.

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