The differential effects of oestrogens and progestins on vascular tone

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The purpose of this paper is to present reported findings of the effects of ovarian steroids on vascular tone. The medical literature was reviewed for relevant contributions. Oestrogen replacement therapy in postmenopausal women is associated with a reduction in mortality from coronary artery disease. Many different cellular actions have been described which help explain the cardioprotective effects of oestrogens, and among these are effects on vascular tone. Oestrogens induce vasodilation through mechanisms involving the arterial endothelium and through endothelial-independent actions. Progestins have varying effects on arterial tone, including induction of vascular smooth muscle relaxation as well as induction of smooth muscle constriction. The effects of oestrogens and progestins on vascular tone are clinically meaningful. Pathophysiological arterial conditions, including angina pectoris and migraine headaches, have been associated with oestradiol deficiency and improvement has been associated with oestradiol replacement. Women with coronary artery disease show improved arterial vasodilator responses after oestradiol treatment which can be reduced by the addition of progestin treatment. Androgens are also vasoactive. Study of the effects of ovarian hormones on vascular tone has become an important area for basic and clinical research.

Key words: arterial tone/cardio-protection/nitric oxide/oestradiol/progestins

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Introduction

Part of the explanation for the cardioprotective effects of oestrogen replacement therapy lies in the actions of oestrogens, which help maintain vasomotor tone and arterial diameter and promote vasodilator reserve capacity and vasomotor stability. Progesterone and progestogens have mixed effects on these parameters, although there is increasing evidence that progestogens oppose some of the cardioprotective effects of oestrogens.

Ovarian hormones affect vasomotor tone by modifying the functions of the vascular endothelium and smooth muscle (VSM). Ischaemia, due to VSM constriction, is prevented by VSM relaxation and increased arterial diameter. Vasoconstriction is induced by adrenergic nerves, blood-borne substances and local autacoids. In most blood vessels, the endothelium releases vasodilators which modify the effects of vasoconstrictor substances. Endothelium-derived vasodilators include nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor (EDHF). EDHF is thought to be a cytochrome P-450 metabolite of arachidonic acid. NO appears to be the major endothelium-derived relaxing factor and acts through elevation of cyclic guanosine monophosphate (cGMP) in VSM. Prostacyclin stimulates adenylate cyclase, and EDHF involves the activation of K+ channels (Furchgott and Zawadzki, 1980; Vanhoutte and Mombouli, 1996). Endothelial cells also generate endothelins, the most potent vasoconstrictors known (Yanagisawa et al., 1988). Oestradiol-induced vasodilatation appears to involve many different mediators, including NO, prostacyclin, calcium ions, endothelin suppression and effects on the synthesis, release and uptake of neurotransmitters including serotonin, epinephrine and norepinephrine. Oestradiol receptors are present in the vascular endothelium and smooth muscle (Horwitz and Horwitz, 1982) and appear to play an integral role in oestrogen’s effects on vascular tone. Progesterone-induced vasoconstriction appears to involve direct actions of progesterone in VSM and adrenergic nerves and actions secondary to
down-regulation of the oestradiol receptor. The effects of these hormones can be clinically significant (Gerhard and Ganz, 1995).

**Actions of oestrogens affecting vascular tone**

Infusion of oestradiol-17β into a sheep’s uterine artery decreases vascular resistance and increases blood flow over the course of ~30 min (Magness and Rosenfeld, 1989). Pulsatility index, a measure of vascular resistance, decreases in women treated with oestrogens (Bourne et al., 1990), and women receiving intravenous and sublingual oestrogens show decreased coronary and peripheral vascular resistance (Reis et al., 1994; Volterrani et al., 1995).

Oestrogen-enhanced NO production is thought to be the primary molecular mechanism underlying its vasodilator effect. Cell cultures of human endothelial cells showed a rapid increase in NO release in response to physiological concentrations of oestradiol-17β. This action appears to be dependent on oestrogen receptor-mediated mechanisms, as the NO increase was inhibited by an oestrogen receptor antagonist. Nevertheless, the action appears to be non-genomic, as the response was maintained in transcriptionally inhibited cells and involved rapid (10 min) formation of cGMP (Caulin-Glaser et al., 1997). Long-term administration of oestrogen up-regulates NO synthase transcription (Rosselli et al., 1995). Basal vascular NO activity is reduced after menopause and returns to premenopausal levels with oestrogen replacement, and serum nitrate and nitrite concentrations are higher in postmenopausal women receiving long-term oestrogen replacement, suggesting increased NO production (Rosselli et al., 1995).

Oestrogen potentiates endothelium-dependent vasodilator response to acetylcholine (Ach), an action indicating increased NO release. Ovariectomized monkeys receiving oestradiol-17β demonstrated a vasodilator response to Ach, while monkeys not receiving hormone replacement showed a vasoconstrictor response (Williams et al., 1990). The vasodilator response was demonstrated in atherosclerotic monkeys treated with conjugated equine oestrogens and with esterified oestrogens (Williams et al., 1994). In the monkey studies, the addition of progesterone and testosterone did not compromise the vasodilator response to Ach (Adams et al., 1997). However, addition of medroxyprogesterone acetate (MPA) to treatment with conjugated equine oestrogens diminished the beneficial Ach-induced endothelium-mediated dilation (Williams et al., 1994; Adams et al., 1997).

In women, coronary artery diameter measurement and blood flow velocity calculations reflected physiological concentrations of oestradiol-17β acutely and selectively potentiated endothelial-dependent vasodilation (Gilligan et al., 1994a; Collins et al., 1995). Infusion of oestradiol-17β into the coronary artery in women with established atherosclerotic disease showed a coronary vasodilatation response to Ach within 20 min. Prior to the oestradiol infusion, the arteries showed a vasoconstrictor response to Ach. As in the cell culture studies, the rapidity of the response suggests an action involving the oestrogen receptor but not involving genomic mechanisms. Interestingly, men treated with oestradiol-17β infusion did not show the Ach vasodilator response of the women, presumably reflecting less oestriadiol receptor in the men’s arteries (Collins et al., 1995).

Demonstration of the NO-releasing effects of oestrogens has been the main focus of molecular and physiological research during the past decade. Non-invasive techniques include use of ultrasound to monitor brachial artery diameters during reactive hyperaemia. Flow stimulus following a period of arterial occlusion is regarded as an indirect measure of NO release. Oestradiol (Lieberman et al., 1994), ethinyl oestradiol (Reis et al., 1994), conjugated equine oestrogens (Gilligan et al., 1994b) and selective oestrogen-receptor modulators (Herrington et al., 1998) have all shown enhanced NO activity using this technique. Other endothelial effects include oestrogen-enhanced prostacyclin production and suppression of endothelin release (Jiang et al., 1992b; Mendelsohn et al., 1994). Endothelial-independent actions of oestrogens also appear to be significant. For example, oestradiol-17β-induced relaxation in rabbit coronary arteries was equal with and without endothelium, and oestrogen inhibition of calcium influx into guinea-pig cardiac myocytes has been demonstrated (Jiang et al., 1991, 1992c). It has also been demonstrated that human coronary arteries are relaxed by oestrogens through non-endothelium-dependent mechanisms (Chester et al., 1995). These and other findings suggest a calcium antagonistic effect of oestrogen contributing to its vasodilating action (Collins et al., 1993). Oestrogens also modulate catecholamine synthesis and release, an action which may be particularly important in postmenopausal women as changes during the menopause include an increase in serum catecholamines, exaggerated catecholamine response to mental stress and rapid fluctuations in catecholamine concentrations during hot flushes (Hamlet et al., 1980; Ginsburg et al., 1982; Owens et al., 1994).

In addition to contributing to the oestrogen replacement therapy-associated reduction in cardiovascular mortality, the effects of oestrogens on vasomotor tone have proved beneficial in providing symptomatic relief for women with angina and migraine (Magos et al., 1983; Sarrel et al., 1992; Rosano et al., 1996a).

**Actions of progestogens affecting vascular tone**

Progesterone receptors (PR) are present in the arterial endothelium and smooth muscle (Ingemmo et al., 1988), and progesterone has been demonstrated to induce endothelium-independent relaxation of rabbit coronary arteries (Jiang et al.,
However, the addition of progesterone, and especially of the more potent progestogens such as medroxyprogesterone acetate (MPA), to oestrogenized vessels induces vasoconstriction (Sarrel, 1995). Decreased NO release appears to be the primary explanation for this opposing action of progesterone and progestogens.

Studies in ovariectomized monkeys indicate oestrogen potentiation of endothelial-dependent vasodilator response to Ach is inhibited by cyclic MPA and essentially eliminated by continuous MPA (Williams et al., 1994). In these studies, conjugated equine oestrogens administered in the equivalent of human clinical doses did enhance arterial vasodilation in response to Ach but MPA reduced this response by >50%. The decreased vasodilation observed with MPA was not seen with progesterone, suggesting MPA’s more potent down-regulation of oestriadiol receptor as a possible mechanism.

Other studies of ovariectomized monkeys showed hyper-reactive vascular muscle cells with prolonged increases in intracellular Ca\textsuperscript{2+} and protein kinase C that correlated with exaggerated in-vivo coronary artery vasoconstrictor responses. The hyperreactive Ca\textsuperscript{2+} responses were abolished when the monkeys received oestradiol-17\textbeta  or progesterone. However, when treated with MPA, the vascular muscle cells remained hyperreactive to vasoconstrictor stimuli, suggesting MPA negated the protective effects of the oestrogen (Minshall et al., 1998). Minshall et al. (1998) measured steroid receptors and reported oestradiol-17\textbeta  up-regulation of oestriadiol receptor and progesterone receptor (PR) in vascular muscle cells but MPA down-regulation of PR expression. In other studies using ovariectomized monkeys, animals receiving oestradiol-17\textbeta  with progesterone or MPA were exposed to pathophysiological stimulation (Miyagawa et al., 1997). Progesterone plus oestradiol protected the monkeys from vasospasm, but when MPA was administered in place of progesterone, the animals all developed a coronary vasospastic response to the stimulus. The authors concluded ‘MPA in contrast to progesterone increases the risk of coronary vasospasm’ (Miyagawa et al., 1997). Supporting these findings is the recent report that the addition of micronized progesterone did not attenuate the vasodilator effect of oestradiol on brachial arteries in postmenopausal women (Gerhard et al., 1998). These authors used high-resolution brachial artery ultrasound before and after reactive hyperaemia as a measure of endothelial function. However, there is evidence that progesterone released during the menstrual cycle can down-regulate oestrogen receptor and compromise vasodilator response. Studies in young women show evidence for maximal NO production during the mid to late follicular phase, with decreased effects during the withdrawal of hormones at the time of menstruation (Kawano et al., 1996).

Studies of MPA effects in women indicate addition of MPA to oestrogen treatment increases forearm vascular resistance (Sullivan et al., 1995), inhibits oestrogen-induced vulva blood flow (Sarrel, 1990), increases cerebral artery resistance (Sarrel et al., 1995), inhibits oestrogen-induced aortic vasodilation (Giraud et al., 1996) and can be associated with myocardial ischaemia (Rosano et al., 1996b; Sarrel, 1997). The clinical significance of continuous MPA administration combined with oestrogen is reported in The Heart and Estrogen/progestin Replacement Study (HERS). A total of 2763 women with established coronary artery disease were randomized to treatment with conjugated equine oestrogens continuously combined with MPA or to a placebo treatment (Hulley et al., 1998). The women receiving continuous/combined treatment showed a marked increase in myocardial infarction, coronary heart disease death and venous thrombosis and embolism during the first 2 years of treatment.

A brief comment about actions of androgens affecting vascular tone

This presentation has focused on the effects of oestrogen and progestins on vascular tone. It is also important to recognize that ovarian androgens are also vasoactive steroids and arterial actions of androgens in women (and men) may be clinically significant. Rabbit coronary arteries treated with testosterone show a vasorelaxant response (Yue et al., 1995). Studies of testosterone effects on vasoreactivity in cynomolgous monkeys show neither a compromising nor an additive effect on oestrogen-induced vasodilator responses (Honore et al., 1996). Recent studies indicate testosterone infusion into coronary arteries in men with coronary artery disease induces vasodilation (Beale et al., 1997), and intravenous administration of testosterone reduced exercise-induced ischaemic response in men with coronary artery disease (Rosano et al., 1997). These actions indicate that testosterone does not have the compromising effects on oestrogen-induced vasodilatation of progestogens but instead may enhance the oestrogen effects. Testosterone effects on vascular tone may be due to direct actions of the hormone, or possibly to aromatization of testosterone to oestradiol, as aromatase has been identified in the arterial wall (Diano et al., 1997). There is also evidence that methyltestosterone combined with esterified oestrogens may have arterial vasodilating effects. Addition of methyltestosterone to esterified oestrogen replacement therapy in postmenopausal women showed an enhanced response in vaginal blood flow (Sarrel and Wiita, 1997). Because methyltestosterone is not aromatized to oestradiol, other mechanisms of androgen action have been suggested. In the study reported (Sarrel and Wiita, 1997), significant lowering of sex hormone-binding globulin among the women receiving combined methyltestosterone and esterified oestrogens was thought to lead to higher levels of free steroids (androgens and oestrogens), with a resultant additive effect on vasodilation.
Conclusions

Oestrogens act in arteries to enhance vasodilator capacity. As emphasized in the recommendations of the 1997 ESHRE Capri Workshop on Hormones and Cardiovascular Diseases, the effects of the oestrogens used in hormone replacement therapy upon vascular tone are complex, involve endothelium-dependent as well as endothelium-independent mechanisms and overall appear to be beneficial (ESHRE Capri Workshop Group, 1998). These effects, along with many other oestrogen effects in the circulatory system, help explain the cardioprotective results reported for oestrogen replacement therapy (Gerhard and Ganz, 1995). Progestrone and, more significantly, progestogens oppose the effects of oestrogens on arterial tone and appear to induce vasoconstrictive responses which may be clinically significant. Androgens act more like oestrogens with respect to arterial tone, which may reflect direct actions of the hormones or a result of aromatization to oestrogens.

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