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Influences of female reproductive hormones on sympathetic control of the circulation in humans

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The significant increase in cardiovascular disease risk with the loss of estrogen and progesterone at menopause has lead to increasing interest in the cardiovascular influences of female reproductive hormones. In addition to direct influences of estrogen to promote endothelium-dependent vasodilation, recent evidence demonstrates important influences of both estrogen and progesterone on the neural control of the peripheral circulation. These influences have been studied in two general contexts. First, the effects of these hormones on the sympathetic control of the cutaneous circulation have received substantial attention. The control of neurogenic vasodilation in the skin in response to hyperthermia is shifted to higher and lower internal temperatures by progesterone and estrogen, respectively. Reflex vasoconstrictor control of skin blood flow is shifted to higher internal temperatures when the hormones are elevated. Second, reproductive hormones have recently been shown to significantly alter sympathetic neural control of the skeletal muscle circulation. Sympathetic neural control of the skeletal muscle circulation (measured directly as muscle sympathetic nerve activity [MSNA]) is altered by hormone status such that resting MSNA is decreased by estrogen, as is the MSNA response to exercise. Furthermore, the baroreflex control of MSNA is significantly modified by estrogen and progesterone. Therefore, female reproductive hormones have widespread influences on the sympathetic control of the circulation in humans. The individual influences of estrogen and progesterone often antagonize one another, and when both hormone concentrations are increased, the net effect probably depends on their relative concentrations and bioactivity. The mechanisms responsible for these influences and their health-related implications deserve further attention.

Key words: estrogen, progesterone, skin blood flow, muscle blood flow, baroflex.

Over the past several decades, it has become clear that female reproductive hormones, especially estrogen, exert crucial protective influences on the cardiovascular system. When this protection is lost at menopause, the risk of cardiovascular disease increases dramatically. This increased risk can be mitigated by the use of hormone replacement therapies [1]. While the influence of female reproductive hormones on the risk for cardiovascular disease is unequivocal, the underlying physiologic mechanisms remain less clear. A large part of estrogen's protective effect stems from a beneficial effect on plasma lipoprotein profiles. Additionally, the influences of estrogen to promote endothelium-dependent vasodilation have been well described and are the subject of several reviews [1–3].

Less well examined is the emerging idea that estrogen and progesterone alter reflex cardiovascular regulation via the autonomic nervous system. This system can alter heart rate, blood pressure, and organ blood flow within one or very few heartbeats. In this review, the influences of female reproductive hormones on the sympathetic neural control of the peripheral circulation will be explored. Most of the information in this area comes from two general areas of research, which will be the focus of this review. First, evidence will be examined concerning the influences of female reproductive hormones on the sympathetic control of the cutaneous circulation. Second, recent evidence concerning the influences of estrogen and progesterone on sympathetic control of the skeletal muscle circulation will be reviewed. The emphasis will be on evidence from integrative studies in humans.

Sympathetic control of the cutaneous circulation

The reflex control of the cutaneous circulation is unique in humans because, in addition to adrenergic vasoconstrictor nerves, it includes a neurogenic vasodilator system [4–6]. Sympathetic vasoconstrictor nerves in the skin are tonically active, and increases and decreases in their activity are responsible for the subtle alterations in skin blood flow that occur with normal daily activities [4]. These small changes in skin blood flow help maintain stable internal temperature during minor changes in environment or physical activity. The vasoconstrictor system is also responsible for the

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marked cutaneous vasoconstriction with environmental cold exposure.

The sympathetic vasodilator system in human skin has the capacity to increase skin blood flow 20- to 30-fold, up to as much as 6–8 L/min during severe hyperthermia. Under such conditions, this neural system controls as much as 60% of the cardiac output [7]. Unlike the vasoconstrictor system, however, the vasodilator system does not exhibit resting tone, and is only active during increases in internal temperature, such as those due to environmental heat stress or exercise [4–6].

Although the existence of neurogenic vasodilation in human skin has been recognized since the early 1930s [6], its mechanism is not entirely understood. The onset of active vasodilation usually occurs at about the same time as the onset of sweating. However, it is not clear to what extent these phenomena are mechanistically linked. For example, cholinergic muscarinic receptor blockade (which completely inhibits sweating) does not inhibit active vasodilation. However, recent evidence suggests that active vasodilation occurs via cholinergic nerve co-transmission [5].

Neural control of skin blood flow via the vasodilator and vasoconstrictor systems is further modified by reflexes associated with exercise and blood pressure regulation [4,8]. For example, both branches of the neural control of skin blood flow are under baroreflex control, so that a fall in arterial pressure can cause an increase in sympathetic vasoconstrictor activity and a reduction in vasodilator activity [8]. This is especially important during hyperthermia, when large percentages of cardiac output and blood volume are directed to the skin. In addition to these acute modifiers, cutaneous vascular control is also influenced by circadian rhythm, heat acclimation, exercise training, and, in women, reproductive hormone status.

Influences of female reproductive hormones

The influences of female reproductive hormones on neural control of blood flow were first noted in the context of their influences on body temperature regulation. Body temperature increases by 0.3–0.5°C in the luteal phase of the menstrual cycle, when progesterone and estrogen concentrations are increased, as compared with the early follicular phase when plasma concentrations of these hormones are low (Fig. 1). Individually, estrogen and progesterone lower and raise body temperature, respectively [9–12]. An early series of studies [10] demonstrated the influence of estrogen in lowering, and of progesterone in increasing, body temperature by simply injecting these hormones into male subjects and measuring body temperature responses. More recently, Stachenfeld *et al.* showed that administration of a progestin alone caused an increase in body temperature [11]. Increases in estrogen concentrations alone, either endogenously [12] or with estrogen replacement therapy [9,13], decrease body temperature. However, when both hormone concentrations are increased in the mid-luteal phase [14–16] body temperature is increased. In the luteal phase, therefore, it appears that progesterone has the dominant

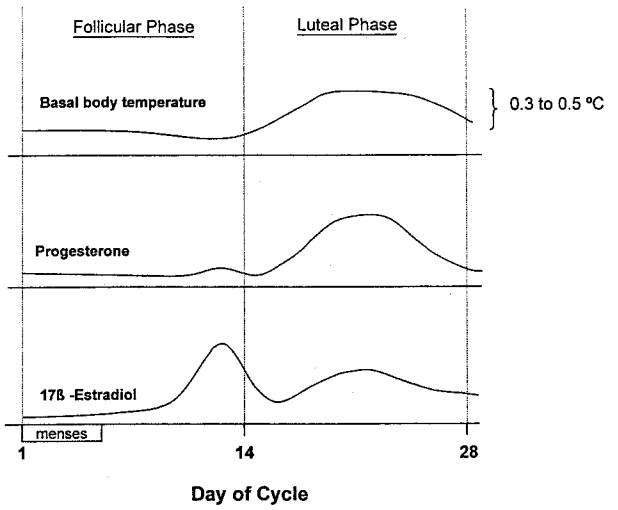

Figure 1. Time course of changes in progesterone, estradiol, and basal body temperature over the course of the human menstrual cycle. Basal body temperature increases 0.3 to 0.5°C in the mid-luteal phase as compared with the early follicular phase. Note that the change in body temperature in the luteal phase is coincident with the increases in progesterone and estradiol.

"thermogenic" effect and promotes the maintenance of a higher body temperature.

In the last 20 years it has become clear that the increase in body temperature in the luteal phase is the result of a regulated shift in reflex thermoregulatory control [14–18]. For example, when body temperature, sweating, and skin blood flow were measured during exercise, the internal temperatures ("thresholds") at which sweating and cutaneous vasodilation were initiated were elevated by about 0.3–0.5°C in the mid-luteal phase compared with the early

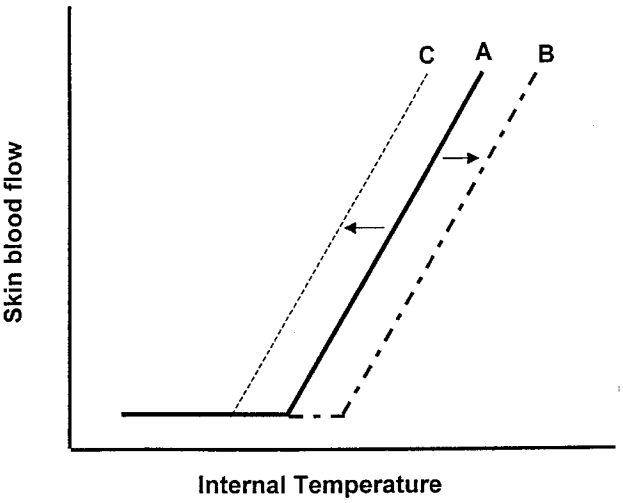

Figure 2. Skin blood flow as a function of internal temperature. **A.** Control condition. Note sharp increase in blood flow following internal temperature threshold for vasodilation. The sensitivity of the response refers to the post-threshold slope of this relationship. **B.** Increased threshold for vasodilation, such as in the luteal phase of the menstrual cycle or with oral contraceptives. Note that skin blood flow is lower at any given internal temperature compared with control condition. **C.** Increased estrogen (eg, estrogen replacement therapy). Note lower threshold for vasodilation such that skin blood flow is higher for any given internal temperature compared with the other two conditions.

follicular phase (Fig. 2) [14,15,18]. Recent evidence gives some insight into the neural mechanisms by which these hormones influence skin blood flow control.

Influences on vasodilator neural control of skin blood flow

As mentioned previously, the onset of reflex cutaneous vasodilation is altered in the luteal phase of the menstrual cycle and the entire vasodilator response is shifted to higher internal temperatures (Fig. 2B). Since there are both vasodilator and vasoconstrictor nerves in the skin, this shift in threshold could be a result of either augmented vasoconstrictor activity or inhibited vasodilator activity [19].

In a recent study [19], we tested the hypothesis that the shift in the threshold for reflex cutaneous vasodilation is caused by a shift in the control of the active vasodilator system to higher internal temperatures. We also tested whether the shift in cutaneous vascular control seen in the normal ovulatory menstrual cycle occurs with the exogenous estrogen and progestin in oral contraceptives. We studied women taking combination (estrogen + progestin) oral contraceptives. Each woman was studied twice, once at the end of the third week of hormone pills (high-hormone phase), and once at the end of the week of placebo pills (low-hormone phase). Our experiments involved selective inhibition of the vasoconstrictor system in a small area of skin, using local application of bretylium (by iontophoresis; 0.6 cm^2). Since adrenergic vasoconstrictor nerves are presynaptically inhibited by bretylium, local treatment with this drug permits the vasodilator nerves to be studied in isolation. Comparison with an adjacent, untreated site allows for the assessment of the contribution of vasoconstrictor nerves. Whole-body heating experiments were conducted with the subjects at rest in a supine position, using water-perfused suits to control body temperature.

Using this approach, we found that the shift in threshold for reflex vasodilation seen in the luteal phase of the menstrual cycle also occurred with the exogenous progestin and estrogen of oral contraceptives [19]. In women with normal menstrual cycles and in those taking oral contraceptives both, this shift was seen at control and bretylium-treated sites (where only the vasodilator system was intact); the magnitude of the shift was similar at both sites. This indicates that most or all of this shift in threshold to a higher internal temperature was a result of a shift in control of the vasodilator nerves [19].

During the luteal phase of the menstrual cycle and during the high-hormone phase of oral contraceptive use, estrogen and progesterone are elevated simultaneously. The observed effects on skin blood flow control, therefore, could be a result of one or the other of the hormones, or a result of their activity in combination. Some insight into this question comes from studies [9,11,12,20] in which cutaneous vascular control and temperature regulation were assessed when either estrogen or progesterone was elevated alone. Brooks *et al.* [9] and Tankersley *et al.* [13] studied perimenopausal and postmenopausal women and compared individuals not taking hormone replacement therapy with those taking estrogen alone (ERT). They showed that ERT had a stimulatory effect on cutaneous vasodilation during exercise, as shown by a shift in the threshold for cutaneous vasodilation to lower body temperatures (Fig. 2C). That is, cutaneous vasodilation began at lower body temperatures (by about 0.4°C) during ERT compared with without ERT [9,13]. Using bretylium administration similar to the aforementioned, Brooks *et al.* showed that the threshold for active cutaneous vasodilation was shifted to lower internal temperatures with ERT [9]. Furthermore, estrogen replacement did not alter resting or maximal skin blood flow [21], suggesting that the altered control of blood flow caused by these hormones is probably not secondary to structural changes in the cutaneous vessels.

These investigators also studied women who were taking combined estrogen + progesterone hormone replacement [9]. In these subjects, the threshold for vasodilation was higher than that in the estrogen alone group, but was not different from individuals taking no hormone replacement.

Although the individual influences of estrogen and progesterone on skin blood flow control in young women have not been specifically studied, indirect evidence suggests that these influences are similar to those seen in the perimenopausal population. Stachenfeld *et al.* [11] found that women taking progestin-only pills had higher resting body temperatures and higher thresholds for sweating than they did when their hormone concentrations were low. However, when the subjects took estrogen + progestin formulations, body temperature and sweating thresholds were not different than when the hormones concentrations were low. Stephenson and Kolka [12] noted that the internal temperature threshold for sweating was lower in the preovulatory phase of the menstrual cycle (when estrogen concentrations are high and progesterone low) compared with the early follicular phase (when both hormones concentrations are low). Although neither study included the measurement of skin blood flow, the internal temperature thresholds for sweating and cutaneous vasodilation are usually similar, and female reproductive hormones appear to have similar influences on both [13–15,19,22]. Taken together, these data [9,11–13] suggest that estrogen alone shifts the threshold for neurogenic cutaneous vasodilation to a lower internal temperature, and that progesterone alone shifts the threshold to a higher internal temperature.

The idea that estrogen and progesterone have opposing influences on skin blood flow and thermoregulation is supported by studies of the activity of single neurons in the preoptic/anterior hypothalamic area of rat brain slices [16,17]. These studies showed that the central control of thermoregulation is altered to promote heat dissipation in the presence of high estrogen [17] and heat conservation/generation in the presence of high progesterone [16].

The net influence of combined estrogen and progesterone is somewhat inconsistent, however. We [19,22,23] and others [24] found that the elevated progestin + estrogen in oral contraceptives caused a shift in body temperature and thermoregulation to a level higher than that seen with low-hormone status. Brooks *et al.* [9] and Stachenfeld *et al.* [11] showed no net influence of the combined hormones on

thermoregulation relative to low-hormone status. The discrepancy may relate to differences among study populations in relative concentrations and bioactivity of estrogen and progesterone.

It is also interesting to note that the influences of estrogen and progesterone on resting body temperature, and on the control of sweating and heart rate during hyperthermia [9,18,19], are all similar in magnitude and direction to the shift in control of the active vasodilator system [19]. Since these changes are similar to the thermoregulatory changes associated with an infection-induced fever, we wondered whether the mechanisms for the thermoregulatory influences of female reproductive hormones are the same as those of a fever [22]. Because, in a fever, the thermoregulatory control shift is prostaglandin-dependent [25], we used systemic cyclooxygenase inhibition (oral ibuprofen) to test this hypothesis [22]. Ibuprofen had no influence on the thermoregulatory control shifts seen with reproductive hormones, indicating that the shift in sympathetic active vasodilation in the skin seen with these hormones is prostaglandin-independent [22]. Similarly, Brooks-Asplund *et al.* [20] recently used systemic aspirin administration to demonstrate that the shifts in temperature regulation seen with hormone replacement therapy in postmenopausal women are independent of prostaglandins. Therefore, the mechanisms for the changes in thermoregulatory control caused by female reproductive hormones differ from those caused by fever.

In addition to internal temperature threshold, another important parameter of reflex cutaneous vasodilation is its sensitivity with respect to internal temperature. The sensitivity refers to the post-threshold slope of the relation between skin blood flow and internal temperature during hyperthermia (Fig. 2). In general, female reproductive hormones do not appear to affect this sensitivity [9,18,19, 22]. However, Hessemer and Brück [14,15] reported an increase in cutaneous vasodilator sensitivity in the luteal phase of the menstrual cycle. The reason for this discrepancy is unknown, but deserves clarification, because changes in sensitivity can result in substantial differences in the level of skin blood flow for a given level of internal temperature.

Influences on vasoconstrictor neural control of skin blood flow

As previously mentioned, tonic activity of sympathetic vasoconstrictor nerves in the skin maintains body temperature during slight variations in environment and activity level [4]. For example, a higher level of resting sympathetic vasoconstrictor activity in the skin would result in lower skin blood flow and less heat dissipation, and therefore higher body temperature. The influences of female reproductive hormones on resting body temperature led us to wonder whether these hormones alter the activity of the vasoconstrictor system. However, the increase observed in resting body temperature in the luteal phase or with oral contraceptives is usually 0.5°C or less. Therefore, the magnitude of the change in skin blood flow required is probably immeasurably small (2% or less [26]). Rather than attempt to measure changes in resting skin blood flow that may be below the resolution of available measurement techniques, we studied the control of the vasoconstrictor system over a range of whole-body skin temperatures [23]. This was done by progressively decreasing skin temperature (using water-perfused suits) in a ramp fashion for 15 minutes. The resulting vasoconstriction gave us an index of the sensitivity of the vasoconstrictor system with respect to mean skin temperature. We also assessed where the control of the vasoconstrictor system was set relative to internal temperature. We found that the sensitivity of the vasoconstrictor system with respect to skin temperature was not altered by hormone status. However, the control of the system was shifted to higher internal temperatures when levels of progesterone + estrogen were elevated [10].

In summary, the individual influences of progesterone and estrogen appear to be to increase [10,11] and decrease [9,12,13], respectively, the body temperature thresholds for cutaneous vasodilation. The net influence when both hormones concentrations are increased is less consistent, although progesterone seems to have the dominant effect in the luteal phase of the menstrual cycle [14,15,18] and often does with combined oral contraceptives [19,22–24]. The threshold changes represent shifts in the control of the sympathetic active vasodilator system [19], and are a part of a central shift in the control of thermoregulation that is prostaglandin-independent [20,22]. Progesterone and estrogen generally do not influence the sensitivity (slope) of active vasodilation with respect to internal temperature [9,18,19,22]. With combination oral contraceptives, the control of the vasoconstrictor system in the skin is shifted to higher internal temperatures, with no influence of these hormones on its sensitivity relative to changes in skin temperature [23].

Sympathetic control of the skeletal muscle circulation

In addition to their influences on the neural control of skin blood flow, female reproductive hormones may also modify sympathetic control of the skeletal muscle circulation. This is a relatively new area of inquiry, and while evidence is limited, recent findings provide some insight and lead to provocative new questions.

In humans, sympathetic vasoconstrictor neural control is the predominant mechanism of control of blood flow to resting skeletal muscle. Currently, a common method for the assessment of sympathetic control of the skeletal muscle circulation in humans is the direct measurement of sympathetic neural outflow to skeletal muscle using peroneal nerve microneurography (ie, muscle sympathetic nerve activity [MSNA]) [32].

Reproductive hormone influences on resting muscle sympathetic nerve activity and muscle vascular resistance

Minson *et al.* measured MSNA and calf blood flow in women in the early follicular and mid-luteal phases of the menstrual cycle [27]. They found that resting MSNA was increased when endogenous progesterone and estrogen concentrations were increased in the mid-luteal phase but that

calf blood flow, vascular resistance, and mean arterial pressure at rest were not affected by menstrual cycle phase [27]. Ettinger *et al.* showed that MSNA at rest was not different between early follicular (low estrogen, low progesterone) and preovulatory (high estrogen, low progesterone) phases of the menstrual cycle [28]. These investigators did not measure calf blood flow. Taken together, these results suggest that progesterone may cause an increase in resting MSNA [27], because the MSNA increase was absent when estrogen alone was increased [28]. Furthermore, estrogen's direct effect to promote vasodilation [3] may have offset the higher MSNA seen by Minson *et al.*, resulting in no net increase in calf vascular resistance in the luteal phase [27].

In a second study, Minson *et al.* showed that resting MSNA is not different between the high-hormone and low-hormone phases of combined oral contraceptives [29]. However, in this study, calf blood flow was higher with high-hormone status, calf vascular resistance tended to be lower, and mean arterial pressure was lower. These findings are also consistent with the idea that a direct vasodilator effect of the hormones (probably estrogen) [2,3] offsets the vasoconstrictor effect of a given level of sympathetic nerve activity. The authors suggested that a difference in the ratio of estrogen to progestin between the two groups (oral contraceptive users and non-oral contraceptive users) may have been the cause of the difference in results between the two studies. This suggestion is consistent with the idea that estrogen (inhibitory) and progesterone (excitatory) have different and perhaps opposing effects on resting MSNA.

Influences on muscle sympathetic nerve activity responses to sympathoexcitation

Exercise causes sympathetic activation and vasoconstriction in vascular beds including nonexercising skeletal muscle. A common model used to study this sympathoexcitation involves isometric exercise of the forearm (handgrip exercise), with simultaneous measurement of sympathetic neural outflow to the calf (nonworking muscle). Ettinger *et al.* [28] tested whether differences in estrogen concentrations during the normal menstrual cycle would influence MSNA responses to exercise in women. They showed that MSNA responses to isometric handgrip exercise were attenuated during the preovulatory phase of the menstrual cycle, when estrogen is increased, as compared with the early follicular phase, when both estrogen and progesterone concentrations are low [28].

In those studies it is possible that estrogen's direct vasodilator influence [2,3] affected the washout of metabolic by-products of muscle contraction by increasing blood flow in the contracting muscle. In this scenario, the stimulation of chemosensitive afferents (metaboreceptors), which cause a reflex increase in MSNA, would be altered. To test this possibility, Ettinger *et al.* [28] used post-handgrip circulatory arrest to stop the washout of the metabolites and measure the MSNA response to metabolite accumulation in the absence of the exercise itself. They observed that the MSNA response to the first minute of postexercise ischemia was attenuated in the high-estrogen phase relative to the early follicular phase (low estrogen, low progesterone concentrations). However, this difference no longer existed in the second minute of post-exercise ischemia. They also studied the MSNA responses to ischemic handgrip exercise. When blood flow is arrested during exercise, there is no washout of metabolites, and they observed no difference in the MSNA responses to ischemic exercise between low and high estrogen status. These observations were taken by the investigators to mean that blood flow was necessary to observe the estrogen-mediated difference in MSNA. The influence of estrogen, therefore, may have been to increase local blood flow in the muscle, perhaps via augmented endothelium-dependent vasodilation [3]. Because the MSNA response to a cold pressor test was not altered by estrogen status, the authors' observation, that estrogen inhibited sympathetic outflow, is specific to the handgrip exercise protocol they used, and not a general effect on sympathoexcitation [28].

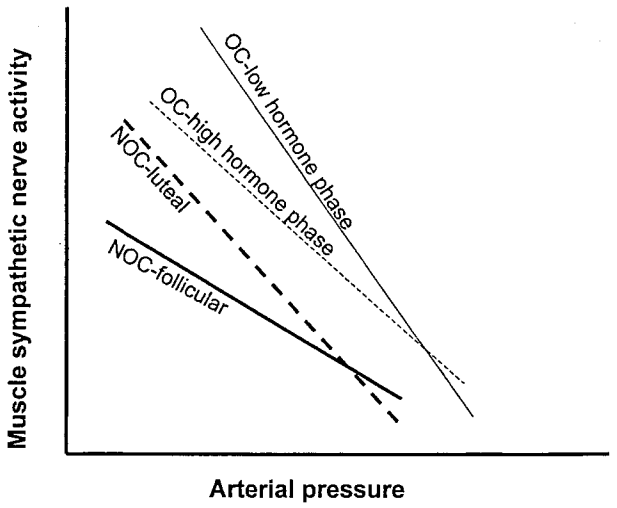

Figure 3. Baroreflex control of muscle sympathetic nerve activity in women in different conditions of reproductive hormone status. The slope of the relationship represents baroreflex sensitivity. In individuals taking oral contraceptives (OC), high-hormone status resulted in a *decreased* sympathetic baroreflex sensitivity. In individuals not taking oral contraceptives (NOC), high-hormone status (luteal phase) resulted in an *increased* sensitivity of the sympathetic baroreflex. See text for discussion. (Adapted from references 27 and 29).

Influences on baroreflex control of muscle sympathetic nerve activity

To test whether female reproductive hormones alter baroreflex control of MSNA, Minson *et al.* conducted studies in women with regular menstrual cycles [27], and in women taking oral contraceptives [29]. They tested the hypotheses that increased estrogen/progesterone status would augment sympathetic and cardiovagal baroreflex sensitivities. To do this, they evaluated MSNA and heart period (R-R interval) during the depressor and pressor responses to sequential bolus injections of sodium nitroprusside followed by phenylephrine. The sensitivity of the sympathetic baroreflex response was assessed by plotting MSNA as a function of arterial pressure. Similarly, the sensitivity of the cardiovagal baroreflex control of heart rate was assessed by plotting R-R interval as a function of arterial pressure. The slope of these

relations was reported as an index of baroreflex sensitivity. They then tested whether the transduction of sympathetic activity into vascular resistance is altered by hormone status, by analyzing vascular resistance in the calf as a function of muscle sympathetic nerve activity.

In women with normal ovulatory menstrual cycles, Minson *et al.* [27] found that sympathetic baroreflex sensitivity was augmented in the mid-luteal phase of the menstrual cycle, such that a given change in arterial pressure caused a larger change in MSNA when the hormones were increased (Fig. 3). Surprisingly, in oral contraceptive users, high-hormone status had the opposite effect: in these subjects, sympathetic baroreflex sensitivity was *decreased* in the high-hormone phase as compared with low-hormone status (Fig. 3) [29]. There was no influence of menstrual cycle phase on the transduction of sympathetic activity into vascular resistance [27]. The influence of hormone status on the baroreflex control of heart rate was similarly dependent on whether the hormones were endogenous or exogenous. In women taking oral contraceptives, cardiovagal baroreflex sensitivity was augmented with high-hormone status [29], while in women with regular menstrual cycles, there was no effect of hormone status on the sensitivity of this arm of the baroreflex [27].

The reasons for the seemingly disparate findings between oral contraceptive users and nonoral contraceptive users are not entirely clear. The authors suggested that the difference in results between the two populations may relate to the differences in the bioactivity and relative concentrations of estrogen and the progestin in oral contraceptives compared with those that occur in the normal ovulatory menstrual cycle [29]. In rats, for example, estrogen enhances sympathetic baroreflex sensitivity [30] whereas progesterone reduces sympathetic baroreflex sensitivity [31]. The dominant effect, therefore, may reside with the hormone with the higher plasma (or central nervous system) concentration or bioactivity, or in some other interaction between the hormones. Furthermore, the alterations in blood pressure regulation by these hormones may be even more profound when combined with the effects of aging, such as occurs in menopausal women. Clearly, more research is needed in humans in this important area.

Summary and conclusions

Female reproductive hormones have substantial influences on the control of the peripheral circulation by the sympathetic nervous system. In general, estrogen's influence on neural control appears to be consistent with its direct influences on the vasculature to promote vasodilation. In support of this idea are the observations that unopposed estrogen promotes reflex vasodilation in the skin via activation of the vasodilator system and inhibits muscle sympathetic neural responses to exercise. By contrast, progesterone appears to promote vasoconstriction. This is seen in its "thermogenic" effect in terms of skin blood flow control. The influences of these hormones on baroreflex control of muscle sympathetic nerve activity are less clear, but include alterations in baroreflex sensitivity. The net effect of the combined hormones may depend on the relative concentrations of estrogen and progesterone in the circulation, as well as on differences in central versus peripheral effects. In terms of skin blood flow, progesterone often has the dominant effect when both hormones are increased, resulting in a shift in skin blood flow control to higher internal temperatures (eg, luteal phase of the menstrual cycle). Further identification of individual mechanisms for these effects and interactions will prove challenging, because their influences at different levels probably interact with and/or offset each other (eg, central versus peripheral effects). These influences could have profound consequences for body temperature and blood pressure regulation, especially when combined with the effects of aging or of disease on these regulatory processes.

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