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New insights into the effects of age and sex on arterial baroreflex function at rest and during dynamic exercise in humans

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Abstract

The arterial baroreflex (ABR) performs an important role in regulating blood pressure (BP) both at rest and during exercise, by carefully orchestrating autonomic neural activity to the heart and blood vessels. Reduced ABR sensitivity (i.e., gain) is associated with increased cardiovascular risk, cardiac electrical instability and orthostatic intolerance, while ‘normal’ ABR function during exercise is important for ensuring an appropriate cardiovascular response is elicited. Previous studies examining the influence of age and sex on resting ABR function in humans have primarily used pharmacological methods (e.g., modified Oxford technique) to change BP and alter baroreceptor input. With this approach only reflex control of heart rate and sympathetic nerve activity may be evaluated, and as such the influence of age and sex on ABR control of BP *per se* remains incompletely understood. Furthermore, the majority of previous studies examining ABR function during exercise have principally assessed young men. Whether these findings can be extrapolated to young women or older men and women remains unclear. Recently the potential for age and sex to modulate the integrative neural control of the cardiovascular system is becoming appreciated. This review article will provide a detailed update of such recent advances into our understanding of the effects of age and sex on ABR control of BP both at rest and during dynamic exercise in humans.

Keywords

ovarian hormones; carotid baroreflex; blood pressure; estrogen; arterial baroreceptors

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Introduction

The arterial baroreflex (ABR) plays a critical role in the short-term regulation of arterial blood pressure (BP) via adjustment of autonomic neural activity directed to the heart and vasculature. Notably, reduced ABR sensitivity has been associated with increased cardiovascular risk (La Rovere et al., 2008), cardiac electrical instability (Chen et al., 2006) and orthostatic intolerance (Mattace-Raso et al., 2007). Despite some early evidence to the contrary (Bristow et al., 1971), it is also now well established that the ABR remains functional during exercise (Bevegard et al., 1966; Potts et al., 1993; Raven et al., 2006; Raven et al., 1997), and plays an important role in ensuring an appropriate neural cardiovascular response is elicited (Walgenbach et al., 1983). In addition, a properly functioning ABR is important in maintaining the electrical stability of the heart (Billman, 2006). Of note, the majority of work examining the ABR in humans, particularly during exercise, has been performed in young men. Whether such findings are representative of ABR responses in young women or older men and women remains unclear. This review will focus on recent advances in our understanding of age and sex-related differences in ABR function both at rest and during dynamic exercise in humans.

Techniques for assessing ABR function in humans

There are multiple methods available for assessing ABR function in humans and the relative merits of such approaches and apparent absence of a 'gold standard' methodology, have been highlighted in several reviews (Cooper et al., 2009; Fadel et al., 2003; La Rovere et al., 2008) and therefore will only be mentioned briefly here. Perhaps due in part to its clinical utility and ease of application, a popular means of estimating ABR sensitivity is by examination of the dynamic relationship between 'spontaneous' beat-to-beat fluctuations in BP and heart rate or muscle sympathetic nerve activity (SNA) (Pagani et al., 1988; Parati et al., 1988; Sundlof et al., 1978). Although this approach provides a useful indicator of ABR sensitivity around the prevailing BP (i.e., operating point of the full baroreflex function curve) it cannot be used to provide a complete assessment of the full ABR stimulus-response relationship (Fisher et al., 2007; Ogoh et al., 2005). Traditionally, human ABR function has been assessed using administration of vasoactive drugs to raise and lower BP (e.g., phenylephrine and sodium nitroprusside) with concomitant measurement of the reflex changes in heart rate and/or muscle SNA (Rudas et al., 1999; Smyth et al., 1969). A limitation of this method, and indeed 'spontaneous' methods, is that ABR control of BP *per se* cannot be determined. However, such a limitation may be circumvented by use of the variable pressure neck chamber technique to acutely elicit carotid baroreceptor perturbation and assess the corresponding systemic BP response (Ernsting et al., 1957; Gribbin et al., 1971). This approach may be used to assess both the magnitude and temporal pattern of the BP, heart rate, muscle SNA, cardiac output, and vascular conductance responses to carotid baroreflex loading (simulated hypertension) and unloading (simulated hypotension) (Fadel et al., 2003). Furthermore, the relative contributions of cardiac output and vascular conductance to a given carotid baroreflex mediated change in BP can be interrogated (Kim et al., 2011; Ogoh et al., 2002a; Ogoh et al., 2003). Finally, due to its non-invasiveness, this technique is well suited for use in a wide range of population groups and can be used reliably both at rest and during exercise (Potts et al., 1993). In light of these advantages this has been a regularly utilized method in our laboratory to examine the potential influences of age and sex on ABR function at rest and during dynamic exercise. With the use of the variable pressure neck chamber to selectively describe carotid baroreflex control the assumption is made that the aortic baroreflex operates in parallel with the carotid baroreflex and therefore, will respond similarly (Raven et al., 1997).

Age and resting ABR function

Ageing is associated with a plethora of alterations in cardiovascular morphology, function and regulation (Lakatta, 1993). With increased age, a decrease in cardiac parasympathetic nerve activity (Davies, 1975; Stratton et al., 2003) and a reduction in cardiac ABR sensitivity (Ebert et al., 1992; Fisher et al., 2007; Gribbin et al., 1971; Matsukawa et al., 1996; Matsukawa et al., 1998) have been consistently identified. Although increases in resting SNA in older individuals are also well characterised (Hogikyan et al., 1994; Seals et al., 2000), whether ageing modifies ABR regulation of vasoconstrictor muscle SNA remains equivocal, with impaired, preserved, and enhanced responsiveness reported in older individuals (Davy et al., 1998; Ebert et al., 1992; Jones et al., 2001; Matsukawa et al., 1996; Matsukawa et al., 1998; Studinger et al., 2009). Furthermore, Abboud and colleagues in dogs (Hajduczuk et al., 1991b), and Seals and colleagues in humans (Jones et al., 2003), indicated that ageing is associated with impaired ABR control of BP. However, other studies have reported a preserved ABR control of BP at rest in older compared to younger subjects using brief (Shi et al., 1996) and pulsatile (Brown et al., 2003) changes in carotid sinus pressure using the variable pressure neck chamber technique. The reason for these disparate findings is not clear but may have to do with the different methodological approaches used to assess ABR function.

In a recent investigation our laboratory group used the variable pressure neck chamber technique to derive full carotid baroreflex stimulus-response curves in young and older individuals at rest (Fisher et al., 2010). In addition, the magnitude of the changes in BP in response to selective carotid baroreceptor unloading (i.e., simulated carotid hypotension), and loading (i.e., simulated carotid hypertension) were identified. Although we observed no differences between young and older individuals in the maximal sensitivity (i.e., gain) of the modelled carotid baroreflex function curve, older subjects exhibited an attenuated pressor response to simulated carotid hypotension, and an augmented depressor response to simulated carotid hypertension (Figure 1). Furthermore, while in young individuals the operating point was located close to the centre of the reflex function curve (i.e., locus of maximal reflex gain), in the older group the operating point was located away from the centring point towards the reflex threshold and to a locus of reduced gain (Figure 2). These observations are consistent with the recent work of Studinger et al. (Studinger et al., 2009), which demonstrated that compared to young subjects, ABR control of muscle SNA exhibited less of an increase in response to falls in BP evoked by intravenous bolus infusion of sodium nitroprusside (nitric oxide donor) in older individuals, while the sympathoinhibitory response to infusion of the pressor agent phenylephrine (α_1 -adrenergic agonist) was augmented. In addition, similar to our findings for BP, when the muscle SNA responses to rises and falls in BP were combined, no age-related differences in ABR gain were found. Collectively, these findings support the concept that age-related alterations in ABR function are differentially manifested in the reflex responses to rises and falls in BP.

The work of Studinger et al. (Studinger et al., 2009) also provides some further mechanistic insight into the differential BP responses that we observed to carotid baroreflex loading and unloading (Figures 1 and 2). These investigators were able to dissect the relative contribution of age-related changes in the mechanical (the carotid artery pressure–diameter relationship) and neural (the carotid artery diameter–muscle SNA relationship) components of the ABR. It appeared that in response to rises in BP the age-related decrease in carotid artery distensibility (Monahan et al., 2001) and associated impairment in the mechanical component of the ABR, was compensated for by an augmented neural component of the ABR (i.e., more marked sympathoinhibition). However, in response to falls in pressure an augmented neural control of muscle SNA did not obviate the effects of carotid artery stiffening, culminating in a more modest sympathoexcitation in older individuals compared

to younger individuals. While the latter may explain the attenuated pressor response to simulated carotid hypotension that we observed in older individuals, a diminished tachycardic response (Fisher et al., 2007; Gribbin et al., 1971; Monahan, 2007; Monahan et al., 2001), or decreased vasoconstrictor response to the evoked increase in sympathetic outflow (Hogikyan et al., 1994) may also contribute. As such, further work is required to determine whether ageing modifies the relative contributions of central hemodynamics and vascular conductance to the overall control of BP via the ABR.

The focus of the majority of the previous studies examining age-related alterations in ABR function has been on ABR sensitivity (i.e., gain). However, the stability of a physiological control system such as the ABR is dependent upon not only the magnitude of an effector response (i.e., gain), but also the latency or timing of this response. In a recent study, we examined how ageing influenced the temporal pattern of the beat-to-beat changes in heart rate and BP in response to selective loading and unloading of the carotid baroreceptors using the variable pressure neck chamber technique (Fisher et al., 2009). We observed that the time taken to reach the peak heart rate and BP response to carotid baroreceptor loading (i.e., simulated carotid hypertension) was significantly delayed in older individuals compared with a group of younger individuals (35% and 104% slower BP and heart rate responses in older subjects) (Figure 3). In contrast, a similar temporal pattern of response was noted for both heart rate and BP in the groups to carotid baroreceptor unloading (i.e., simulated carotid hypotension). The slower cardiovascular response to carotid baroreceptor loading in older individuals was associated with a reduction in indices of cardiac parasympathetic activity provided from heart rate variability analyses. Furthermore, pharmacological blockade of parasympathetic activity in young individuals resulted in a prolonged timing of the peak responses to carotid baroreceptor loading. Taken together these findings suggest that the more sluggish cardiovascular responses to carotid baroreceptor loading in older individuals may be related to a reduction in cardiac parasympathetic efferent activity.

In summary, recent findings indicate that older individuals exhibit an attenuated pressor response to hypotensive challenges, and an augmented depressor response to hypertensive challenges. This differential responsiveness appears to be manifested by a relocation of the operating point away from the centring point closer to the threshold of the baroreflex function curve, and may be explained by complex age-related alterations in the neural and mechanical components of the ABR. Furthermore, older individuals exhibit a slower cardiovascular response to simulated carotid hypertension, which is associated with age-related reductions in cardiac parasympathetic activity.

Sex, ovarian hormones and resting ABR function

Epidemiological studies demonstrate a lower prevalence of cardiovascular disease and hypertension in young women compared to young men; however, in older post-menopausal women the incidence of hypertension becomes greater than in men of similar age (Thom et al., 2006). These findings highlight the potential protective influence of ovarian hormones. However, the mechanisms by which estrogen and/or progesterone may exert a cardioprotective effect remain incompletely elucidated. Nevertheless, in recent years there has been an increased awareness of the potential for sex-differences in cardiovascular regulation and the potential role played by ovarian hormones.

Several human studies have reported that compared to men, resting cardiac ABR sensitivity is decreased in young women (Abdel-Rahman et al., 1994; Beske et al., 2001; Convertino, 1998; Laitinen et al., 1998). However, other studies have indicated no differences in resting ABR control of heart rate between young men and women (Cooke et al., 2002; Guasti et al., 1999; Lindblad, 1977; Tank et al., 2005). Similarly, whether menstrual cycle phase

influences cardiac ABR sensitivity remains unclear. Minson et al. (Minson et al., 2000) observed no differences in cardiac ABR sensitivity between the mid-luteal and the early follicular phases of the menstrual cycle. However, cardiac ABR sensitivity has been reported to be increased during the late follicular phase compared with the early follicular and mid-luteal phases of the menstrual cycle (Tanaka et al., 2003). We recently used the variable pressure neck chamber technique to derive full carotid baroreflex stimulus-response curves in an attempt to better understand whether sex and/or fluctuations in endogenous ovarian hormones during the menstrual cycle modulate carotid baroreflex control of the heart (Kim et al., 2012). We noted a greater bradycardic response to carotid baroreceptor loading (i.e., simulated carotid hypertension) in young women at the early follicular phase of the menstrual cycle compared to young men. This observation was consistent with a relocation of the operating point away from the centring point towards the reflex threshold on the carotid-cardiac baroreflex stimulus-response curve, meaning that young women appeared to be in a more optimal position to defend against rises in BP. Notably, we did not detect a difference in carotid baroreflex control of heart rate between the early follicular, late follicular and mid-luteal phases of the menstrual cycle. The reason for the conflicting findings of our investigation and those showing increased cardiac ABR sensitivity during the late follicular phase (Tanaka et al., 2003) is unclear but may be related to methods of baroreflex assessment (i.e., non-pharmacological vs. pharmacological approaches).

Results examining the influence of sex on ABR control of muscle SNA at rest are equivocal with studies reporting greater (Hogarth et al., 2007), similar (Tank et al., 2005) or impaired (Christou et al., 2005) sympathetic ABR sensitivity in young women compared to men. A possible explanation for these disparate findings is that variations in ovarian hormone concentrations (i.e., estrogen and progesterone) do not appear to have always been controlled for. In this regard, Minson et al. (Minson et al., 2000) showed that sympathetic ABR sensitivity is elevated during the mid-luteal phase of the menstrual cycle compared with the early follicular phase (Minson et al., 2000). Furthermore, chronic oral estrogen supplementation appears to increase sympathetic ABR sensitivity in post-menopausal women (Hunt et al., 2001b). However, transdermal estrogen replacement therapy was shown not to alter sympathetic ABR sensitivity (Vongpatanasin et al., 2001). Thus, overall, the influence of sex and ovarian hormones on the baroreflex control of sympathetic outflow remains unclear and given the relatively small number of studies performed in this area, requires further investigation. Particularly in light of studies in rats, which have demonstrated that estrogen can enhance resting sympathetic baroreflex sensitivity (He et al., 1998; Saleh et al., 2000).

While it is indeed important to understand the baroreflex-mediated sympathetic nerve response, it is the vasoconstriction-dilation evoked by the change in SNA that is ultimately critical for BP regulation. To begin to understand the end-organ response, we recently examined whether the relative contributions of cardiac output and total vascular conductance to ABR-mediated changes in BP are different in young men and women (Kim et al., 2011). Previous studies in young men have shown that carotid baroreflex-mediated changes in BP are predominantly attributable to alterations in the peripheral vasculature (i.e., total vascular conductance), rather than cardiac output (Ogoh et al., 2002a; Ogoh et al., 2003). Given the strong evidence that vasoconstrictor responsiveness is blunted in young women (Hogarth et al., 2007; Kneale et al., 2000), we hypothesized that BP responses via the carotid baroreflex would be attenuated in women due to smaller changes in total vascular conductance. However, we found that carotid baroreceptor unloading (i.e., simulated carotid hypotension) elicited similar BP responses in both young women and men, which were principally attributable to a change in total vascular conductance in both groups (Kim et al., 2011). Moreover, in response to carotid baroreceptor loading (i.e., simulated carotid hypertension) women actually exhibited an exaggerated reduction in BP compared to men (Figure 4).

Interestingly, this greater depressor response in the women was driven by a much more pronounced bradycardia and reduction in cardiac output than was evident in the men, whereas in the men changes in total vascular conductance made a greater relative contribution to BP control during carotid baroreceptor loading. Thus, it appears that compared to young men, young women rely more on cardiac output for short-term BP regulation via the carotid baroreflex. Whether fluctuations on ovarian hormones across the menstrual cycle influence the dominance of cardiac output in mediating BP responses via the baroreflex in young women requires investigation.

As noted above, the timing of the effector response (i.e., latency) is also important for ABR function. With this in mind, we recently examined the latency to peak heart rate and BP responses to carotid baroreceptor loading and unloading in young men and women (Kim et al., 2011). Although cardiac latency was not different between groups, young women exhibited more rapid BP responses to carotid baroreceptor perturbation, compared to men of a similar age. Indeed, the time taken to reach the peak BP in response to carotid baroreceptor loading (4.7 ± 0.3 women vs. 5.9 ± 0.3 men seconds) and unloading (5.5 ± 0.2 women vs. 6.2 ± 0.2 men seconds) was significantly shorter in young women compared to young men. Although the time to peak heart rate was similar between groups, the more marked cardiac output responses in young women, particularly to carotid baroreceptor loading, may partly explain their more rapid BP response.

Limited studies have investigated whether ABR function is different in older men compared to older women. Recent work by Okada et al. (Okada et al., 2011) reported that although resting cardiac ABR sensitivity was similar in older men and women, sympathetic ABR sensitivity was significantly lower in older women. Interestingly, such sex-differences in sympathetic ABR sensitivity were associated with a stiffening of the barosensory blood vessels (i.e., carotid and aortic arteries). Further studies are required to determine whether such changes are translated into impairments in overall ABR control of BP in older women *per se*. In addition, it is presently unknown whether the relative contribution of vascular conductance and cardiac output to the short-term regulation of BP via the ABR is different between older men and women.

In summary, recent studies have identified pertinent effects of sex and/or ovarian hormone concentration on ABR function in humans. Young women exhibit greater depressor responses to simulated carotid hypertension compared to young men, and appear to rely more on cardiac output than on changes in total vascular conductance for short-term BP regulation via the carotid baroreflex. This may be related to young women having lower resting muscle SNA and sympathetic support of BP (Christou et al., 2005; Ng et al., 1993; Schmitt et al., 2010). In addition, a greater β -adrenergic mediated vasodilatation may minimize the effectiveness of muscle SNA to evoke α -adrenergic mediated vasoconstriction in young women (Hart et al., 2011; Kneale et al., 2000). Nevertheless, young women exhibit more rapid BP responses to carotid baroreceptor perturbation compared to young men. Further studies are needed to better elucidate the interactions between age and sex on ABR control of BP.

Age, exercise and ABR function

During exercise the ABR is reset in an exercise-intensity dependent manner and functions with preserved maximal sensitivity, around the prevailing BP and heart rate (Bevegard et al., 1966; Coote et al., 1976; Papelier et al., 1994; Potts et al., 1993). ABR resetting with exercise results from the independent and interactive effects of “central command”, neural signals arising from higher brain centres (Gallagher et al., 2001; Iellamo et al., 1997; McIlveen et al., 2001; Ogoh et al., 2002b), and the “exercise pressor reflex”, sensory

feedback from group III and IV afferents within exercising skeletal muscles in response to metabolic and mechanical provocation (muscle metaboreflex and mechanoreflex) (Fisher et al., 2008; Iellamo et al., 1997; McIlveen et al., 2001; Smith et al., 2003). In addition, recent studies indicate that cardiopulmonary baroreceptors provide further modulation of ABR resetting during exercise (Fadel et al., 2012; Ogoh et al., 2007; Volianitis et al., 2004). Given that central command, the exercise pressor reflex and the cardiopulmonary baroreflex, can affect ABR function, it is not prudent to simply extrapolate age-related differences in resting ABR function to exercise. Indeed, the exercise pressor reflex has been suggested to be attenuated in older individuals (Markel et al., 2003), and an age-related alteration in central command (Carrington et al., 2002) and the interaction between the cardiopulmonary baroreflex and ABR (Hajduczuk et al., 1991a; Shi et al., 1996) have also been indicated.

Given the importance of ABR control of the heart during exercise (Billman, 2006; Walgenbach et al., 1983), and the paucity of information pertaining to the influence of age, we used the variable pressure neck chamber technique to derive full carotid baroreflex stimulus-response curves for the control of heart rate at rest and during dynamic exercise (leg cycling at 50% heart rate reserve) in young and older healthy subjects (Fisher et al., 2007). Although carotid-cardiac baroreflex resetting occurred in both young and older subjects, the magnitude of resetting was much greater in older subjects. Furthermore, a striking ~50% reduction in the maximal gain and responding range of the carotid baroreflex was noted in older subjects compared to younger subjects both at rest and during exercise. Collectively, these findings are indicative of an age-related reduction in the ability to regulate heart rate by the baroreflex both at rest and during dynamic exercise. The underlying mechanisms are unclear but possibly include mechanical (i.e., reduced aortic and carotid arterial compliance) and neural (i.e., altered baroreceptor afferent output or conduction, central integration, efferent autonomic activity, and/or end organ responsiveness) ABR components (Chapleau et al., 1995; Hunt et al., 2001a; Monahan et al., 2001).

There is evidence that proper functioning of the ABR is of fundamental importance for an appropriate cardiovascular response to exercise. In exercising dogs, acute baro-denervation leads to an exaggerated increase in BP (Walgenbach et al., 1983). An emerging concept is that the baroreflex acts to partially restrain the BP response to exercise, by buffering increases in SNA produced by activation of central command and the exercise pressor reflex (Joyner, 2006). Thus, impaired ABR (i.e., decreased maximal gain) may mean that the increases in muscle SNA during exercise cannot be effectively limited. This unrestrained increase in SNA would potentially have two important functional consequences. First, the greater sympathetically-mediated vasoconstriction would contribute to a larger increase in BP. Second, greater vasoconstriction within the exercising skeletal muscle would potentially limit the increases in perfusion necessary to meet the metabolic demands of the exercise. As such, it has been suggested that a diminished baroreflex function may not only lead to an augmented BP response to exercise, but could also potentially limit exercise tolerance (Joyner, 2006; O'Leary, 2006).

It is possible that age-related impairments in ABR function could contribute to the exaggerated BP during exercise commonly reported in older individuals (Daïda et al., 1996; Fisher et al., 2007; Ogawa et al., 1992; Stratton et al., 1994). Therefore, we used the variable pressure neck chamber technique to determine full carotid baroreflex function curves, in order to test the hypothesis that the carotid baroreflex control of BP would be impaired in older individuals during exercise (Fisher et al., 2010). Although we had previously elucidated the influence of age on carotid baroreflex control of heart rate, a separate determination of carotid baroreflex control of BP was required because the limbs of the baroreflex controlling the heart and vasculature do not always function in a parallel fashion

(Rudas et al., 1999). We observed that during exercise the magnitude of the upward and rightward resetting of the carotid baroreflex-BP stimulus response curve was 40% greater in older individuals (Figure 2). Furthermore, despite maximal carotid baroreflex gain being similar in young and older individuals the operating point was repositioned further away from the centring point and towards the reflex threshold in the older group. Although this relocation of the operating point may mean that there is a reduction in the ability of the carotid baroreflex to protect against a fall in BP with advanced age, the capacity to respond to a hypertensive stimulus appeared greater in older individuals. As such, it seems that an impairment in the maximal gain of the carotid baroreflex control of BP does not explain the exaggerated BP responses to exercise in older individuals. Further studies are required to elucidate the mechanism(s) underlying the exaggerated pressor responses to exercise commonly observed in older individuals including but not limited to increased arterial stiffness (Lakatta, 1993), impaired metabolic vasodilatation (Schrage et al., 2007) and exaggerated sympathetic vasoconstriction (Dinenno et al., 2006; Fadel et al., 2004).

Collectively, these studies indicate that during exercise older individuals exhibit a greater upward and rightward resetting of the carotid baroreflex stimulus-response curves for the control of both heart rate and BP, when compared to younger individuals. In addition, notable reductions in carotid baroreflex control of heart rate are evident in older individuals both at rest and during exercise. Furthermore, although maximal gain for the carotid baroreflex control of BP appears to be well maintained in older individuals under these conditions, attenuated pressor responses to hypotensive challenges and greater depressor responses to hypertensive challenges are manifest at rest and during exercise in older subjects.

Sex, ovarian hormones and ABR function during exercise

Recent evidence suggests that estrogen can attenuate both central command and the exercise pressor reflex (Ebert et al., 1992; Ettinger et al., 1998; Hayes et al., 2002; Schmitt et al., 2003), which as indicated above, are key contributors to ABR resetting during exercise. Given these findings, we investigated whether sex and/or physiological fluctuations in ovarian hormone concentration could modulate ABR resetting and function during dynamic exercise (Kim et al., 2012). We found that the magnitude of carotid baroreflex resetting for the control of heart rate and BP was not different in young men and women (Figure 5). Furthermore, the magnitude of carotid baroreflex resetting during exercise was similar in young women when studied at the early follicular, late follicular and mid-luteal phases of the menstrual cycle (Figure 6). This suggests that physiological fluctuations in ovarian hormones across the menstrual cycle are insufficient to affect carotid baroreflex resetting during exercise. However, it does not preclude the effects of sustained hormone replacement therapy, such as that used in postmenopausal women, on ABR function during exercise. Limited work has been conducted in older postmenopausal women examining the neural control of the cardiovascular system during exercise, and a thorough examination of the influence of estrogen and estrogen-progesterone interactions on muscle SNA and BP responses to exercise as well as baroreflex function is warranted in this population.

Although physiological fluctuations in endogenous ovarian hormone concentrations do not appear to modulate ABR resetting during dynamic exercise, a greater pressor response to simulated carotid hypotension was noted at rest and during exercise in the young women when progesterone and estrogen concentrations were both elevated (mid-luteal phase) compared to the early follicular and late follicular phases. This observation supports the concept that progesterone may modulate muscle SNA responses via the ABR (Minson et al., 2000). In addition, women exhibited greater reductions in heart rate in response to simulated carotid hypertension at rest and during exercise, and this more marked ABR-mediated

bradycardia was persistent throughout the menstrual cycle. Consistent with this greater bradycardia to hypertension, the operating point of the carotid-cardiac function curve was observed to be located further away from the reflex centring point towards the threshold, in young women at all phases of the menstrual cycle, both at rest and during exercise. Furthermore, the expected movement of the operating point towards the threshold of the carotid-cardiac function curve during exercise was more marked in young women compared to young men.

Overall, our recent studies indicate that the magnitude of carotid baroreflex resetting during exercise does not appear to be influenced by sex or physiological fluctuations in ovarian hormone concentrations across the menstrual cycle. However, women exhibit greater carotid baroreflex-mediated heart rate control, specifically in response to simulated carotid hypertension; an effect that appeared to be mediated by the operating point of the carotid-cardiac function curve being located away from the centring point towards the threshold of the full baroreflex function curve. Future studies are required to delineate the potential effects of sex and/or ovarian hormone concentration on the relative contribution of cardiac output and total peripheral conductance to overall ABR control of BP both at rest and during dynamic exercise in humans.

Conclusion

The majority of previous work examining ABR function, particularly during exercise, has been performed in young men. However, recently there have been a number of advances in our understanding of the independent and interactive effects of age and sex as well as fluctuations in ovarian hormones on ABR function in humans. Consideration of multiple facets of ABR function in addition to the traditional composite assessment of ABR sensitivity, such as consideration of the temporal pattern of the response (i.e., latency), the differential responses to hypotension and hypertension, and the relative contribution of central (cardiac output) and peripheral (vascular conductance) factors to ABR-mediated BP regulation, have provided valuable insights into age and sex-related differences in ABR function in humans.

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Figure 1.

Mean BP responses to neck pressure (panel A; +40 Torr) and neck suction (panel B; -80 Torr) in young ($n=15$, 22 ± 1 years) and older ($n=11$, 61 ± 2 years) subjects at rest and during moderate intensity leg cycling (50% heart rate reserve). Values are means $\pm$ standard error. P values indicate results of 2-way analysis of variance. Reproduced with permission from (Fisher et al., 2010).

Figure 2.

Modelled carotid baroreflex function curves for the control of BP determined using the variable pressure neck chamber technique in young ($n=15$, 22 ± 1 years) and older ($n=11$, 61 ± 2 years) subjects at rest and during moderate intensity leg cycling (50% heart rate reserve). Open symbols denote older subjects and filled symbols represent young subjects. Symbols denote centring points (squares), operating points (triangles), carotid sinus pressure thresholds (circles), and carotid sinus pressure saturations (upside-down triangles). Values are means $\pm$ standard error. Reproduced with permission from (Fisher et al., 2010).

Figure 3.

Temporal pattern of mean BP and heart rate responses to acute carotid baroreceptor unloading (panel A; neck pressure, NP) and loading (panel B; neck suction, NS) in one young subject (closed circles) and one older subject (open circles). Arrows denote peak responses. Reproduced with permission from (Fisher et al., 2009)

Figure 4.

Percentage change in total vascular conductance (TVC; panel A) and cardiac output (CO; panel B) at the time of the mean BP nadir elicited with acute neck suction (-60 Torr; carotid baroreceptor loading) in 20 young women (20 ± 1 years) and 20 young men (20 ± 1 years). Panel C shows the calculated relative contribution of total vascular conductance and cardiac output to the fall in BP elicited by neck suction. Values are means $\pm$ standard error. * denotes a significant difference from women ($P < 0.05$, t -test). Reproduced with permission from (Kim et al., 2011).

Figure 5. Modelled carotid baroreflex function curves for the control of BP, along with the maximal gain (G_{MAX} ; panel a), the operating point gain (G_{OP} ; panel b) and the operating point minus the centring point ($OP-CP$; panel c), in young women ($n=18$, 22 ± 0.4 years) and young men ($n=16$, 21 ± 0.4 years) at rest and during moderate intensity leg cycling (50% heart rate reserve). Symbols denote centring points (squares), operating points (triangles), carotid sinus pressure thresholds (circles), and carotid sinus pressure saturations (upside-down triangles). Values are means $\pm$ standard error. P values indicate results of 2-way analysis of variance. Reproduced with permission from (Kim et al., 2012).

Figure 6.

Modelled carotid baroreflex stimulus response curves for the control of BP, along with the maximal gain (G_{MAX} ; panel a), the operating point gain (G_{OP} ; panel b) and the operating point minus the centring point ($OP-CP$; panel c) at rest and during moderate intensity leg cycling (50% heart rate reserve), in young women ($n=10$) at three different phases of the menstrual cycle. Symbols denote centring points (squares), operating points (triangles), carotid sinus pressure thresholds (circles), and carotid sinus pressure saturations (upside-down triangles). EF, early follicular; LF, late follicular; ML, mid-luteal. Values are means $\pm$ standard error. P values indicate results of 2-way analysis of variance. Reproduced with permission from (Kim et al., 2012)