Effect of Aging on Baroreflex Function in Humans

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Abstract

Arterial blood pressure (BP) is regulated via the interaction of various local, humoral, and neural factors. In humans the major neural pathway for acute BP regulation involves the baroreflexes. In response to baroreceptor activation/deactivation, as occurs during transient changes in BP, key determinants of BP such as cardiac period/heart rate (via the sympathetic and parasympathetic nervous system) and vascular resistance (via the sympathetic nervous system) are modified to maintain BP homeostasis. In this review, the effects of aging on both the parasympathetic and sympathetic arms of the baroreflex are discussed. Aging is associated with decreased cardiovagal baroreflex sensitivity (i.e., blunted reflex changes in R-R interval in response to a change in BP). Mechanisms underlying this decrease may involve factors such as increased levels of oxidative stress, vascular stiffening, and decreased cardiac cholinergic responsiveness with age. Consequences of cardiovagal baroreflex impairment may include increased levels of BP variability, an impaired ability to respond to acute challenges to the maintenance of BP, and increased risk of cardiac sudden death. In contrast, baroreflex control of sympathetic outflow is not impaired with age. Collectively, changes in baroreflex function with age are associated with an impaired ability of the organism to buffer changes in BP. This is evidenced by the reduced potentiation of the pressor response to bolus infusion of a pressor drug after compared to before systemic ganglionic blockade in older as compared to young adults.

Keywords: autonomic nervous system, blood pressure, baroreceptor
Arterial blood pressure (BP), the product of cardiac output and systemic vascular resistance, is regulated acutely and chronically through various local, humoral, and neural factors. Neural regulation of BP occurs via tonic and reflexive modulation of autonomic nervous system outflow (both sympathetic and parasympathetic nervous system). Acutely, changes in these outflows influence key determinants of BP such as cardiac chronotropy (sympathetic and parasympathetic) and inotropy (sympathetic) as well as vascular resistance (sympathetic) in many vascular beds. In response to frequently encountered physiological stressors that challenge the maintenance of BP, such as orthostasis (35), meal ingestion (65), or exercise (105), severe persistent hypotension results in individuals with an impaired ability to reflexively engage the autonomic nervous system (e.g., autonomic failure). These data illustrate the critical role the autonomic nervous system exerts on acute BP regulation (particularly reflexive). The primary mechanism by which BP is rapidly and reflexively modulated in humans is via the baroreflexes (28, 62, 97). The aim of this review is to present scientific evidence that aging is associated with alterations in baroreflex function, which in turn are associated with functional changes in BP control.

The baroreflexes are neurocardiovascular reflexes that operate in a negative feedback fashion, in an attempt to maintain circulatory homeostasis. The baroreflex loop anatomically originates at the level of the baroreceptors. The baroreceptors are highly specialized stretch-sensitive nerve endings distributed throughout various regions of the cardiovascular system such as the carotid artery, aorta, and the cardiopulmonary region, which transmit neural impulses associated with their activation/deactivation to the central nervous system. Baroreceptors located in the carotid artery and aorta are sometimes referred to as “arterial” or “high-pressure” baroreceptors and those in the cardiopulmonary areas as “cardiopulmonary” or “low-pressure”
baroreceptors. After transmission of afferent impulses to the central nervous system signals are integrated and the efferent arm of the reflex projects neural signals systemically via the sympathetic and parasympathetic branches of the autonomic nervous system. Generally, in response to increased firing rate of the baroreceptors (as occurs during a transient increase in systemic BP) efferent sympathetic outflow is inhibited (reducing vascular tone, cardiac chronotropy, and cardiac inotropy) and parasympathetic outflow is increased (reducing cardiac chronotropy). The opposite occurs when BP decreases (Fig. 1).

It is through influences exerted on determinants of BP that baroreflexes contribute to short-term (i.e., beat-to-beat) BP regulation (28, 62, 97). In contrast, the role of the baroreflexes in establishing long-term (i.e., resting) levels of BP is less apparent (22). This journal recently published a series of Invited Reviews (6, 55, 86, 114) and an Editorial Focus (13) on this topic. The remainder of this review will focus on the role of the baroreflexes in short-term BP regulation.

Due to vast amount of experimental data on the topic of age-associated changes in baroreflex function, discussion will focus on the most pertinent findings and data from human studies will be emphasized. Additionally, due to extreme difficulty and possible ambiguity involved in trying to isolate the effects or contributions of specific baroreceptor populations (i.e., arterial and cardiopulmonary baroreceptors) in humans (50, 88, 112), data presented will represent “integrated” baroreflex responses (i.e., to involve contributions from both cardiopulmonary as well as arterial baroreceptors). Lastly, the strengths and weaknesses associated with various methods to assess baroreflex function will not be addressed, as this has previously been done (28, 62). Generally methods to assess baroreflex function rely on observing the body’s response (output) to forced (such as occurs during vasoactive drug infusions) or
naturally occurring (such as naturally occurring oscillations in BP) changes in baroreceptor input.

**Cardiovagal Baroreflex Sensitivity (BRS)**

The cardiac arm of the baroreflex involves baroreflex-mediated prolongation or shortening of cardiac period in response to changes in baroreceptor input (commonly a change in BP). If examined over a wide range of BP’s, a sigmoid relation between cardiac period (response) and BP (stimulus) is revealed (Fig. 1) (26). The linear portion of this stimulus-response curve is used to quantify cardiovagal BRS (Fig. 1 and Fig. 2). In individuals with blunted cardiovagal BRS a smaller change in cardiac period occurs in response to a given change in BP (i.e., the stimulus-response curve is less steep). The term cardiovagal is used to indicate that the measured response is directed toward the heart and is vagally mediated. The latter point is confirmed experimentally by the demonstration that atropine abolishes the bradycardic response to an acute increase in BP (27). Cardiac period (R-R interval) is regressed against systolic BP and not heart rate as the former has been shown experimentally in dogs to be linearly related to changes in cardiac-vagal nerve traffic (44).

*Importance of Reflexive Cardiovagal Control Beyond BP Control*

A compelling body of experimental evidence has accumulated, which indicates that measures of reflexive cardiovagal control such as cardiovagal BRS provide prognostic information regarding the risk of sudden cardiac death (9, 10). Prospective studies in humans after acute myocardial infarction support the link between low cardiovagal BRS and increased risk of sudden cardiac death (48, 49). Data assessing the prognostic ability of cardiovagal BRS
measured before myocardial infarction to identify individuals at risk of sudden cardiac death after myocardial infarction are needed. As aging is associated with an increased incidence of sudden cardiac death (43) decreased levels of cardiovagal BRS with age, if present, may be clinically important.

**Effect of Aging on Cardiovagal BRS**

In the 1960’s a technique was developed which allowed quantification of cardiovagal BRS based on the R-R interval response to transient drug-induced increases in BP (Oxford technique) (106). Shortly after its development several groups used this technique to demonstrate decreased cardiovagal BRS with advancing age (11, 33). Subsequently, a number of studies have confirmed these age-associated reductions using various experimental techniques (25, 37, 51, 73, 75, 76, 78, 90, 95, 109) (Fig. 3). Cardiovagal BRS is inversely and linearly correlated with subject’s age (r=-0.65-0.69) (51, 73).

Additionally, cardiac slowing during sustained increases in BP (such as those induced by steady-state infusion of vasoactive drugs) is also blunted with age (41). As chronotropic response to such BP changes includes a significant sympathetic component (46) these data suggest that this aspect of baroreflex function also is impaired with age. Moreover, as BRS derived from methods employing rapid transient changes in BP (i.e., Oxford technique) and steady-state changes in BP do not correlate with one another suggests that these methods may test or provide information on separate aspects of baroreflex function (107).

All of these previously mentioned studies have been cross-sectional in nature. Accordingly, limitations associated with such data (e.g. survival bias, lifestyle differences,
subject differences present at baseline, etc.) should be kept in mind when these data are considered.

**Mechanisms Underlying Age-Associated Declines in Cardiovagal BRS**

Changes in any segment of the cardiac baroreflex arc (afferent arm, central integration, and efferent arm) may contribute to age-related decreases in cardiovagal BRS. In humans we are limited in our ability to dissect out points along the baroreflex arc that may function differently with advancing age. For instance, it is unknown if a given baroreceptor stimulus induces a similar change in afferent activity in young and older adults. Data from animal studies suggests that it may be reduced with age (2).

Additionally, it has been suggested that arterial stiffening within barosensory containing segments, such as the carotid artery and aorta, may contribute to baroreflex dysfunction with age. This is based on the observations that arterial stretch is a key determinant of baroreflex activation (3) and that aging is associated with decreased arterial compliance (5) in barosensory containing regions. This arterial stiffening may reduce the stimulus (arterial stretch) applied to baroreceptors during a given change in BP resulting in blunted baroreflex-mediated changes in cardiac period in older adults. Correlations between carotid arterial compliance measured at rest and cardiovagal BRS across subjects varying widely in age are consistent with the concept that arterial stiffening contributes to age-associated reductions in cardiovagal BRS in humans (73). Additionally, several studies have examined the possibility that arterial stiffening contributes to impaired cardiovagal BRS with age by examining alterations in carotid arterial properties during spontaneous (47) as well as drug-induced changes in BP (37, 78). These studies expressed cardiovagal BRS conventionally (ΔR-R interval/Δsystolic BP) as well as in a manner that
removes the process of transducing changes in BP into arterial deformation (Δ R-R interval/Δ carotid diameter). Impairment in this latter expression would strongly suggest the presence of a neural deficit in the baroreflex arc with age. Collectively, the results of these studies indicate that both arterial stiffening (37, 78) as well as neural deficits likely contribute to age-associated reductions in cardiovagal BRS (37, 47).

Central integration of barosensory information (afferent-efferent coupling) can only be studied in animals for technical reasons. Previously, the ability of the baroreflexes to rapidly inhibit renal sympathetic nerve activity (SNA) was reported to be well-preserved with age in dogs (34). However, there appeared to be an “escape” from this inhibition over even brief periods of time (34). This escape was evidenced by an inability of sustained increases in carotid sinus pressure to maintain inhibition of renal SNA in older dogs (34). In contrast renal SNA was consistently inhibited throughout the duration in which carotid sinus pressure was elevated in young dogs (34). Importantly, escape from baroreceptor restraint of SNA in older dogs appeared to be explained by rapid adaptation of central pathways and not by reduced input from baroreceptors (34). It is important to emphasize that these deficits were noted on the efferent sympathetic pathway and effects on the efferent vagal pathway were not tested. Future studies addressing this latter issue are needed.

The final step in the baroreflex arc involves changes in efferent cardiac-vagal nerve traffic eliciting end organ responses (i.e., alterations in cardiac period). This process involves propagation of neural impulses down the efferent vagal neurons, ganglionic transmission, release of acetylcholine into the synaptic cleft at the sinoatrial node, and postsynaptic activation of cardiac muscarinic receptors. Animal models of heart failure have identified defects within the parasympathetic ganglia which contribute to diminished vagal control (8). Whether such effects
also occur in aging is unknown and appears to be an important area of future research. Additionally, there are data that suggest decreased: 1) muscarinic M<sub>2</sub> receptor density (12), 2) cardiac responsiveness to muscarinic receptor activation (92), and 3) prejunctional modulation of acetylcholine release in atria with age (80) in humans. Collectively, any of these factors could contribute to an impaired ability for cardiac-vagal nerve traffic to elicit changes in cardiac period in older adults. Finally, data on a small group of young and older adults suggest the bradycardic response to a cold face test, which causes reflex bradycardia via the same efferent cardiac-vagal pathway as the baroreflex, is preserved with age (79). Although differences were not statistically different (~30% lower in older adults) they may be of physiological significance. These findings need to be confirmed in a larger group of subjects before being widely accepted. Collectively, most but not all information suggest that impairments in the efferent vagal arm of the baroreflex may contribute to age-associated decreases in cardiovagal BRS.

Previously, intravenous infusion of high doses of ascorbic acid (~4-5 grams) were shown to increase cardiovagal BRS in older, but not young adults (76). These data suggested that: 1) oxidative stress contributes to age-associated reductions in cardiovagal BRS and 2) that some critical level of oxidative stress is required to suppress BRS as no effect of ascorbic acid was observed in young adults. The site at which ascorbic acid exerts its effect in humans is unknown, but may involve a direct effect of free radicals on baroreceptor nerve endings (53), a centrally-mediated effect, or an effect on the elastic properties of the large cardiothoracic arteries. The latter effect is unlikely as we previously showed no acute effect of ascorbic acid on carotid arterial compliance in older adults (30). Additionally, it is possible that ascorbic acid decreased the break down of centrally generated nitric oxide by free radicals resulting in increased cardiovagal BRS (108).
**Effect of Aging on Sympathetic BRS**

The sympathetic arm of the baroreflex involves baroreflex-mediated alterations in sympathetic outflow in response to changes in baroreceptor input. If examined over a wide enough range of BP’s a reverse sigmoid relation between sympathetic outflow (response) and BP (stimulus) is revealed (Fig. 1) (94). The linear portion of this curve is used to quantify sympathetic BRS (Fig. 1 and Fig. 2). In individuals with impaired sympathetic BRS a smaller change in sympathetic outflow occurs in response to a given change in BP. Sometimes measures of blood flow or vascular resistance are used as surrogates for sympathetic outflow.

Early studies indicated that forearm vasoconstrictor responses to sustained levels of lower body negative pressure (LBNP) were blunted in older as compared to young adults (17, 40). These observations were used as experimental evidence for baroreflex dysfunction. However, an alternative explanation could be that the baroreceptor stimulus (which is difficult to quantify during LBNP) was less in older adults thus explaining the blunted forearm vasoconstrictor response. A mechanism that could provide support for this alternative hypothesis is age-associated reductions in leg venous compliance/capacitance (52, 74), which would reduce the magnitude of central hypovolemia at a given absolute level of LBNP in older adults (82). Thus, these early studies do not provide definitive insight into the effects of aging on sympathetic baroreflex function.

Most (25, 66, 67), but not all (68), subsequent studies (all cross-sectional) have suggested a preserved ability of the baroreflexes to alter directly recorded efferent sympathetic nervous system outflow directed towards skeletal muscle (MSNA) or plasma norepinephrine (70) in response to acute dynamic changes in BP (i.e., sympathetic BRS) with advancing age (Fig. 4).
Therefore, in contrast to reductions in cardiovagal BRS with age, there is no convincing evidence for age-associated changes in sympathetic BRS. In humans direct recordings of efferent sympathetic outflow directed to only the skin and skeletal muscle (MSNA) can be obtained (116). As only MSNA is under baroreflex control this is the only vascular region in which dynamic regulation of sympathetic outflow has been determined in young and older adults. It is possible that other effects would be observed in other vascular beds.

**Other Measures of Baroreflex Function**

In addition to examining reflexive changes in cardiac period or sympathetic outflow, there are other ways to gain insight into the effects of aging on baroreflex function. One method involves application of negative or positive pressure over the anterior neck to engage and disengage the carotid baroreceptors, respectively. When negative pressure is applied over the anterior neck (i.e., a baroreceptor input is changed) bradycardia, sympathetic withdrawal, and a reduction in BP (i.e., changes in baroreflex output) occurs. The opposite occurs with the application of positive pressure. Using this method it has been shown that the dependent variable, in this case the hypotensive response (decrease in systemic BP) to neck suction is reduced in a group of 31-48 year old compared to 20-30 year old adults (54) suggesting baroreflex impairment. Similar impairments with age have been reported across a wider range of ages, although deficits were transient occurring only in the first few seconds (~15 seconds) of a change in baroreceptor input (61). These data suggest an impaired ability of the baroreflexes to regulate BP with age.

The BP increasing or decreasing effect of many stressors is determined by the interaction of various factors. For instance the net effect of administration of a vasoactive medication is
dependent on at least several critical factors such as the body's sensitivity to a pharmacological substance and any attempt by the baroreflexes to counteract and therefore attenuate any vasoactive effect. The contribution of this latter effect is difficult to determine (i.e., quantify) in humans. However, recently a technique was developed that examines the potentiation of the BP elevating effect of a intravenous bolus of phenylephrine (25 µg) measured before divided by the BP elevating effect of the same drug/dose and after complete systemic ganglionic blockade in humans (61). The resulting potentiation ratio was termed to be an index of in vivo ‘baroreflex buffering.’ The results of this study reported that the BP elevating effect of the phenylephrine bolus was potentiated 6-fold after ganglionic blockade in young healthy subjects and 2-fold in essential hypertensive adults. These data indicate that the ability of the baroreflexes to buffer changes in BP is severely compromised in hypertensive adults compared to young healthy adults. Subsequent studies noted reduced baroreflex buffering with age in humans (41). As the baroreflex buffering response is an integrated response it is determined by the net effect of changes in vascular resistance(s) as well as cardiac output on BP. The relative contributions of these components as well as the time course of these changes to dynamic changes in BP have not been investigated in humans. Collectively, impaired baroreflex buffering and greater autonomic support of basal BP (measured as the absolute decrease in BP at rest after complete ganglionic blockade) in older adults (42), provides strong evidence for altered autonomic nervous system regulation of both basal and reflexive support of BP with age.

Other Modulators of Baroreflex Function

Evidence has accumulated that autocrine/paracrine factors (such as prostacyclin, endothelin-1, nitric oxide, platelet factors, and superoxide) as well as humoral factors (such as
aldosterone and angiotensin II) may exert direct effects on baroreceptors and/or central nervous system pathways to influence normal and contribute to abnormal baroreflex function (15, 16). To date, the role of many of these compounds on age-associated changes in baroreflex function has not been determined. Moreover, numerous factors may modulate baroreflex function via central actions (15). Some substances which may contribute to age-associated alterations in baroreflex function via a central effect include angiotensin 1-7 and angiotensin II (98) and nitric oxide (108).

**Potential Consequences of Altered Cardiovagal Baroreflex Function with Age**

*Effects Independent of Blood Pressure Regulation*

The consequences of impaired cardiovagal BRS with age may be of clinical significance. As previously mentioned, data from human studies (48, 49) support the concept that low levels of cardiovagal BRS contribute to increased incidence of sudden cardiac death after myocardial infarction. Thus, age-associated decreases in cardiovagal BRS may help explain the increased incidence of sudden cardiac death with age (43). Prospective studies addressing whether low levels of cardiovagal BRS predicts sudden cardiac death in the general population are needed.

Cardiovagal BRS and age are inversely related (51, 75) and plasma norepinephrine levels at rest and age are linearly related (99, 123). Shimada and colleagues tested the hypothesis that decreases in cardiovagal BRS with age underlie increases in plasma norepinephrine (104). To test this hypothesis univariate and partial correlational analyses were performed between cardiovagal BRS, plasma norepinephrine and BP in a large group of subjects over a wide age range (14-77 years of age). Analyses revealed significant negative correlations between cardiovagal BRS and age independent of plasma norepinephrine levels. In contrast the relation
between plasma norepinephrine and age was abolished after the effect of cardiovagal BRS was removed by partial correlation analysis. These data do not prove cause-and-effect, but they do provide initial support for the concept that reductions in cardiovagal BRS may contribute to sympathoexcitation with age in humans. These data are important based on the detrimental role sympathetic activation is thought to exert on cardiovascular system function with age (99). In contrast, several animal studies suggest that the direction of this relation may not be similar in rodents (i.e., sympathetic nervous system activation suppresses the cardiovagal arm of the baroreflex) (31, 72). Future studies in humans in which levels of cardiovagal BRS or sympathetic outflow are acutely manipulated would provide further insight into the potential mechanistic link between the strength of the cardiovagal arm of the baroreflex and sympathetic outflow at rest.

Effects which Influence Blood Pressure Regulation

One way to examine the ability of the body to acutely regulate BP is to examine BP variability. Ambulatory monitoring suggests that BP variability increases with age (100, 122, 124). Importantly, these increases may occur independent of age-associated increases in BP (124). Presently, the mechanisms underlying increased ambulatory BP variability with age are unknown. However, several studies have reported that increased ambulatory BP variability is modestly associated with impaired cardiovagal BRS (63, 119) and others have suggested that decreases in cardiovagal BRS contribute to increases in BP variability (38, 60). As ambulatory BP variability is an independent predictor of cardiovascular mortality in the general population (45) understanding the mechanisms underlying its increases are of biomedical importance.

Additionally, BP variability can be assessed on beat-to-beat basis from direct intra-arterial recordings or from non-invasive methods (Finapres or Portapres). Various measures of
BP variability measured on a beat-to-beat basis have been shown to be unchanged (32, 117), increased (59, 60, 89), and decreased (117) with advancing age. Why different results are obtained with these methods is unclear, but several possibilities exist. First, in a number of these previous studies, subjects were studied under supine resting conditions. It is possible that under these strictly controlled conditions that BP variability does not increase with age. Second, previous studies suggest that high vagal modulation of the heart contributes to, rather than buffers BP variability in supine humans (111). This could mask a true aging effect, which may only be present under other conditions (i.e., in upright humans). Lastly, the use of non-invasive BP devices may not accurately depict all expressions of BP variability (83, 84). Collectively, any and/or all of these factors may make it more difficult to detect age-associated changes, if present.

Another issue of physiological importance is whether age-associated impairments in cardiovagal BRS impairs the ability to acutely deal with a challenge to the maintenance of BP. In young adults, cholinergic blockade, which abolishes the ability to rapidly alter heart rate in response to acute changes in BP, potentiates the pressor and depressor responses to several distinct physiological stressors (121). Thus, impaired cardiovagal BRS with age, which in part mimics cholinergic blockade, may produce functional impairments in BP control. This suggestion was confirmed experimentally by the demonstration of a greater hypotensive response to rapid application of central hypovolemic stress in older compared to young adults (103). These impaired responses to hypovolemic stress in older adults were mimicked by cholinergic blockade performed in young adults (103). Collectively, these studies strongly suggest that an impaired ability to rapidly accelerate heart rate via the cardiac-vagal arm of the baroreflexes produces functional deficits in BP control in older adults.
Orthostatic hypotension is defined as a decrease in systolic (>20 mmHg) or diastolic (>10 mmHg) BP from supine levels 3 minutes after assumption of the upright posture (1). The incidence of orthostatic hypotension is of biomedical importance based on its association with increased rates of all-cause mortality (64) as well as that its occurrence may contribute to the increased incidence of falls in the elderly (115). Orthostatic hypotension has been reported to occur in between 3% to >50% of older adults (4, 14, 29, 57, 58, 85, 91, 96) and this incidence may increase with advancing age (96). This wide range in incidence rates likely involves numerous factors such as inclusion of subjects with known co-morbidities, low levels of reproducibility of tests for orthostatic hypotension, differences in experimental controls, varying definitions of orthostatic hypotension, and differences in the timing of key measurements (56, 118). Thus, the true effect of aging devoid of disease on the incidence of orthostatic hypotension is unclear. Small studies performed in humans even suggest that the incidence of falls in BP during orthostatic stress may be reduced with age (113). If the incidence of hypotension does not increase with age it does not suggest that age-associated changes in baroreflex function are not important, but they may rather point to the importance of other compensatory changes in cardiovascular system function that occur, which ‘offset’ changes in baroreflex function (74).

A single study has demonstrated that the magnitude of the decrease in BP from the supine to upright posture (even if not sufficient to be classified as orthostatic hypotension) are associated with lower levels of cardiovagal BRS in older adults (39). These findings are consistent with low levels of cardiovagal BRS being associated with low orthostatic tolerance in other populations (19-21). Additionally, the maintenance of BP in the upright posture may require a larger percentage of an older individuals physiological reserve, which could compromise the ability to deal with additional challenge/stresses to the maintenance of BP. This
suggestion is supported by the observation of more pronounced decreases in BP in older adults during combined orthostatic and postprandial stress (69, 101).

**Consequences of Impaired Baroreflex Buffering with Age**

As previously discussed, baroreflex buffering is reduced with age (41). Such impairment may alter an individual’s responses to administration of vasoactive medications. This occurs as the medications net effect on systemic BP is determined by the body’s sensitivity to the medication as well as any ongoing attempt by the baroreflexes to defend a change in BP. This blunted baroreflex buffering with age could explain why augmented depressor responses to sodium nitroprusside infusion occur in older adults (70, 95, 120) despite similar vascular sensitivity to the drug (24). Thus, caution must be applied in dosing/administering vasoactive drugs in older adults.

**Effect of Gender on Baroreflex Function**

When one considers the effect aging exerts on baroreflex function, potential gender-related effects should be considered. Some studies have reported lower cardiovagal BRS in young (7), middle-aged (36), and older (51) females compared to age-matched males while others have not observed similar effects (109). In either case the relative rates of decline with age appear similar in men and women (51). Mechanism(s) underlying potential gender-related effects on cardiovagal BRS are unclear. In contrast, the effect of gender on sympathetic BRS are less apparent (110). Only 1 (67) of the 4 articles (25, 66, 68) cited in this review determining the effect of aging on sympathetic BRS included women subjects. However, gender specific responses were not presented (67). Thus, we cannot determine if sympathetic BRS is unchanged
with age in women as it appears to be in men (25). A mechanism that could contribute to gender differences in sympathetic BRS, if present, could involve sex hormones (71).

**Effects of Endurance Exercise Training on Baroreflex Function in Older Adults**

The observation that endurance training may alter BP regulation in young adults has stimulated many to examine the effects endurance training exerts on baroreflex function (18, 93). Additionally, the effect endurance training exerts on baroreflex function in older adults has been studied to provide insight into potential mechanisms underlying the cardioprotective effect of regular exercise (87). Cross-sectional studies suggest that: 1) endurance training is associated with greater levels of cardiovagal BRS in older endurance-trained as compared to older sedentary adults (23, 75, 81) and 2) age-associated declines in cardiovagal BRS are attenuated in endurance-trained as compared to sedentary adults (75). Results from longitudinal endurance-training studies support these cross-sectional findings (75, 81). Less is known about the effect endurance training exerts on sympathetic BRS. A single longitudinal study reported that sympathetic BRS was unchanged by 12 weeks of endurance training (3 days/week) (102). Interestingly, an increase in cardiovagal BRS was not observed with training either (102). It is possible that the training stimulus was insufficient to elicit an effect (75). Future cross-sectional studies in older sedentary and endurance-trained adults or longitudinal studies employing a greater training stimulus appear warranted.

**Summary**

In summary, aging appears to be associated with specific and selective impairments in baroreflex function. Impairments in baroreflex function include a decreased ability to alter
cardiac period in response to acute alterations in BP (i.e., cardiovagal BRS) and a decreased ability of the baroreflexes to buffer changes in systemic BP. In contrast, the effect of aging on the ability of the baroreflexes to dynamically alter sympathetic outflow directed towards skeletal muscle in response to acute changes in BP (i.e., sympathetic BRS) is not similarly impaired. Collectively, changes in baroreflex function with age are associated with functional changes in BP control, which include increased levels of blood pressure variability, augmented BP falls during acute central hypovolemic stress, and possible greater incidence of hypotension during application of physiological stressors. The specific mechanisms responsible for these changes in baroreflex function with age are unknown, but may include variables related to the afferent arm (such as vascular compliance and oxidative stress), central processing (such as afferent-efferent coupling and its modulators, oxidative stress, and angiotensin II), and efferent arm (such as sinoatrial node responsiveness to acetylcholine). Lastly, as both gender and endurance-training status may exert important influences on baroreflex function these variables should be considered when interpreting any data on baroreflex function in humans.
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References


Figure Legends

Figure 1. This figure depicts the stimulus-response curves for both the cardiac and sympathetic arm of the baroreflex determined during application of positive and negative pressures over the anterior aspect of the neck in humans. Relations between carotid distending pressure and changes in R-R interval (left figure) and between carotid distending pressure and muscle sympathetic nerve activity (right panel) are presented. Data are the mean responses of 10 trials for each subject at each level of neck pressure and suction. The stimulus variable varies depending on the method used to assess baroreflex sensitivity. In this case the stimulus is carotid sinus pressure (systolic pressure minus neck pressure). Used with permission (94).

Figure 2. Representative data from a baroreflex trial using the modified Oxford technique. In panel A a continuous beat-by-beat recording of the systolic blood pressure (BP; solid line), diastolic BP (dashed line), R-R interval, and muscle sympathetic nerve activity (MSNA) is presented. A bolus intravenous infusion of nitroprusside occurs at minute 0 followed by a bolus infusion of phenylephrine at minute 1. These infusions elicit characteristic decreases and subsequent increases in BP that elicit baroreflex-mediated changes in R-R interval and muscle sympathetic nerve activity (MSNA). In panel B regressions between: 1) R-R interval and systolic BP from the nadir to peak systolic BP response (left graph) and 2) MSNA and diastolic BP (right graph) from the start of the nitroprusside infusion to the peak increase after phenylephrine are presented, based on recommended analysis techniques (95). The linear slopes of these relations are used to quantify cardiovagal and sympathetic baroreflex sensitivity (BRS). Used with permission (77).
**Figure 3.** Cardiovagal baroreflex sensitivity (BRS) values in young (18-37 years old), middle-aged (38-56 years old), and older adults (57-79 years old). Cardiovagal BRS declines from young to middle-aged and from middle-aged to older. Used with permission (75).

* P<0.05 versus young subjects

† P<0.05 versus middle-aged

**Figure 4.** Individual sympathetic baroreflex sensitivities (MSNA BRS) plotted vs. age (left panel). Regression analysis revealed no correlation between the 2 variables. Mean regression lines describing relation between diastolic blood pressure (BP) and total integrated muscle sympathetic nerve activity (MSNA) with baseline values superimposed (right panel). Slopes of regression lines were the same in the 3 groups of subjects although the lines were shifted rightward (to higher levels of BP) and upward (to higher levels of MSNA). The similar slopes between the age groups suggest a preserved ability of the baroreflexes to dynamically and acutely regulate MSNA [sympathetic (MSNA) BRS] with age in humans. Used with permission (25).
Figure 2

A

Blood Pressure (mmHg)

R-R interval (ms)

MSNA

Minutes

B

Cardiovagal BRS

Sympathetic BRS

slope = 20.9 ms/mmHg
r=0.95

slope=-6.3
au/beat/mmHg
r=0.92

Systolic BP (mmHg)

Diastolic BP (mmHg)
Figure 3

![Bar chart showing Cardiovascular BRS (ms/mmHg) for Young, Middle-aged, and Older groups. The chart indicates a significant decrease in Cardiovascular BRS with age, with a p-value of * and a trend with †.](image-url)
Figure 4