Role of Vascular Receptors in the Development of Hypertension in the Elderly Population

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Abstract

Hypertension is a disease common in adults, with many risk factors and potentially life-threatening outcomes. Blood pressure is controlled by receptors that inform the brain about the amount of pressure inside the arteries, and the amount of oxygen and carbon dioxide in the blood, respectively. Research has revealed that baroreflex sensitivity (BRS) decreases with increasing age and that there is a high correlation between hypertension and low BRS. However, various studies with differing results have indicated that high blood pressure is what causes BRS to decline, and vice versa. Several studies have shown very conflicting results on the correlation between chemoreflex and age; there have been indications of chemoreflex having a positive, negative, and zero correlation with age. In several experiments, the surgical removal of the chemoreceptors of hypertensive rats was followed by a decrease in blood pressure. These animal experiments, and an additional noninvasive human experiment in which the chemoreceptors were temporarily "shut off," are reasons why more attention should be given to chemoreceptors as a route of alleviating hypertension.

Keywords
- hypertension
- baroreflex
- chemoreflex
- arterial stiffness
- blood pressure
- age
- elderly

Hypertension is a condition in which there is excess pressure from blood against the artery walls. Hypertension is very common in the United States, with nearly one out of every two adults suffering from the disease.[1] Earlier stages of hypertension may show no symptoms,[2] while later stages of hypertension may be fatal, leading to strokes, heart failure, and/or kidney diseases.[3] While conditions such as a sedentary lifestyle or an unhealthy diet may be causes for hypertension,[2] hypertension has also been found to be greatly correlated with age. Research has shown that the greatest association between age and hypertension is structural changes occurring in the arteries, such as arterial stiffening.[4] However, there are other factors in aging that can cause hypertension. The circulatory system contains specific receptors that function in maintaining normal blood pressure for the body. This literature review focuses on the relationship between age and the functionality of those receptors, and its effects on the pathogenesis of hypertension.

Hypertension

There are three main determining factors of blood pressure: cardiac output, blood volume, and resistance. There are several conditions (mostly relating to an unhealthy lifestyle) that may cause hypertension: for example, a high sodium intake diet, or the development of plaques on arterial walls.

Hypertension is a cause of many life-threatening circumstances. Over time, damage can occur to the arteries, causing them to narrow, leak, or rupture. Blood clots may form due to the formation of plaques. The inability of these vessels to

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properly deliver blood to their required locations may cause strokes, heart attacks, and kidney failure.

Receptors of the Circulatory System

The circulatory system has a variety of receptors it uses to regulate blood pressure. Baroreceptors are located on the carotid sinuses and aortic arch. Baroreceptors send messages to the nucleus of the tractus solitarius (NTS) about the amount of stretch the vessels are experiencing due to blood pressure. Chemoreceptors are located on the carotid bodies and aortic bodies (tissue surrounding the vessels) and send messages to the NTS about the oxygen levels, carbon dioxide levels, and pH of the blood. The NTS can activate the sympathetic system or parasympathetic system, depending on the need. When detecting a blood pressure that is too high, the NTS will activate the parasympathetic system, which lowers the heart rate and stroke volume and causes vasodilation. Low blood pressure would initiate the sympathetic system, increasing the heart rate and stroke volume, and causing vasoconstriction.

Besides the afferent input from the baroreceptors and chemoreceptors used to communicate about blood pressure, the central nervous system continuously modulates the baroreceptor-mediated autonomic tone of the heart and blood vessels.[5,6] Additional research has shown that the nervous system has a set point for blood pressure, based on the NTS receiving impulses from the renin-angiotensin system.[7] On occasions where the body would demand a higher blood pressure (i.e. exercise), the NTS would have to temporarily reset. Damage done to these areas of the brain, due to injury or tumors, may be a cause of chronic elevation of arterial pressure.[8]

Age's Effects on Receptors

As humans age, many of their receptors begin to decline in their functionality. This is commonly associated with the decline of the "five senses" in the elderly, such as the diminished ability to hear or see. When it comes to hearing loss, while there are many possible causes of impairment, the most likely cause is changes in the cochlea, such as loss of hair.[9] Likewise, recent research has found that most of the vision impairment that occurs in the elderly is due to age-related macular degeneration, a progressive disease in which light-sensing cells are damaged in the macula, the part of the retina responsible for central vision.[10] Aside from the five senses, aging may also negatively affect cardiovascular receptors responsible for maintaining healthy blood pressure, the focus of this review.

Aging on Baroreceptors

Already from the 20th century, research was being conducted on the effects of aging on baroreflex sensitivity (BRS). Research as early as 1976 was already coming out with results of a negative correlation between BRS and age.[11] A relatively early study that focused on the relationship between age and functionality of the baroreceptors was conducted by Laitinen et al in 1998.[12] The study was aimed at observing the dependency of BRS on age and gender in healthy subjects and consisted of 117 healthy subjects ages 23 to 77. After the experiment, a significant inverse correlation was found between age and BRS; for male subjects (BRS [in ms/mm Hg] $= 4.16 - 0.035 \times$ age (year); $r = -0.796$, $p < 0.0001$) and in female subjects (BRS (in ms/mm Hg) $= 3.42 - 0.030 \times$ age (year); $r = -0.603$, $p < 0.0001$). They concluded that age and gender together accounted for 52% of interindividual BRS variation, the most important physiological correlates of BRS (after having also measured other factors, such as blood pressure, plasma norepinephrine, epinephrine).

A more recent study, conducted by Man et al, looked at BRS's association with multiple factors in a population, using a sample size of 901.[13] The 2021 study confirmed (after many other studies had also done so) the negative correlation between age and BRS; it was found that BRS would decrease between 0.06 to 0.15 ms/mm Hg per year of aging. A 2017 study focused on BRS changes due to age in a younger population, examining 49 children between the ages of 6 and 14.[14] DiFrancesco et al determined that BRS would increase with age until around 10 to 11 years, which was when BRS would then begin to decrease with increasing age.

A study conducted in 2007 by Fauvel et al explored the relationship between age and BRS by looking at the longitudinal effects of age on BRS, to confirm the many cross-sectional studies which were only able to show the interindividual relationship between age and BRS.[15] The 5-year prospective study consisted of 205 men of ages 18 to 50. The study was able to confirm the inverse relationship between age and BRS and calculated a 3.6% attenuation of spectrally determined BRS per year.

Additional noteworthy information includes studies in the 1990s which specifically looked at how age affected muscle sympathetic nerve activity.[16,17] Both studies concluded that the parasympathetic component of the arterial baroreflex deteriorated with age; however, the sympathetic component was very well maintained, at least until the 7th decade of life.[16] A 2007 study conducted by Monahan et al intended to establish arterial compliance as the underlying mechanism of BRS deterioration.[18] For 47 healthy sedentary men of ages 19 to 76, arterial compliance was measured using the simultaneous application of ultrasonography and arterial applanation tonometry and was compared with age-associated declining of BRS. Carotid artery compliance was found to be positively related to BRS ($r = 0.71$; $p \leq 0.001$), and by itself explained 51% of the variation in cardiovagal BRS. A limitation of this study, however, was that it only focused on sedentary individuals. It is possible that arterial compliance may have less of an association with declining BRS in active or nonsedentary individuals.

Baroreceptors and Hypertension

Baroreflex is known to be the most important nervous regulatory mechanism for maintaining balanced blood pressure.[19] In many of the already mentioned studies,[11–13,18] while investigating the relationship between age and BRS, blood pressure had also been recorded and was found to have a negative correlation with BRS. For example, Laitinen et al

found a strong negative correlation ($p < 0.01$) between both systolic and diastolic blood pressure and BRS.[12] DiFrancesco et al's study[14] was an exception, showing changes in BRS regardless of an increasing or decreasing blood pressure (however, they did not look at the relationship between BRS and blood pressure itself). This is explainable as the population studied was children of ages 6 to 14. A similar exception was found in a study that specifically involved elderly subjects.[20]

There can be multiple explanations behind the inverse correlation between blood pressure and BRS. One is that the high blood pressure is what causes the BRS to decrease; the high blood pressure over time may remodel arterial walls (the location of baroreceptors). The other is that the lowering of BRS is what leads to the increase of blood pressure; miscommunications or lack of communication from the receptors to the NTS may bring about the lack of utilization of the parasympathetic system when needed.

High blood pressure being the cause of a low BRS has been seen in multiple studies. In a 1971 study, Gribbin et al measured the blood pressure and BRS of 81 subjects ages 19 to 66, to study the correlation between blood pressure and BRS.[21] It was found that blood pressure was negatively correlated with BRS. Something very noteworthy was that eight of the subjects who at the time showed relatively lower BRS results, although at the time had normal blood pressure, were known to have had hypertension in the past. The history of high blood pressure may very well explain the low BRS; the high pressure impacted the arterial walls, permanently damaging their receptors. This explanation, however, has a few limitations. The first is the relatively smaller group that had this finding (eight people). The second is that this may be explained in other ways; those subjects may have had a low BRS their entire lives, which was what caused them to become hypertensive in the first place (conducting a longitudinal study would solve this issue).

In 1999, James et al conducted an experiment to learn about the effects of calcium-blocking therapy on cardiovascular homeostasis in elderly subjects with isolated systolic hypertension.[22] The experiment consisted of 6 weeks of therapy with a modified release of nifedipine or a placebo ($n = 14$). Clinic systolic blood pressure (but not diastolic) had been reduced by nifedipine (by 14 ± 6 mm Hg; $p = 0.03$). During treatment, BRS significantly increased ($p < 0.05$). At the end of the study, James et al explained that a direct effect of relaxing the smooth muscle around the baroreceptors and reducing the "splinting" effect is what may have increased the BRS. They also considered that a diminished BRS in subjects with isolated systolic hypertension had traditionally been attributed to arteriosclerosis and arterial rigidity, conditions not readily reversible using short-term hypertensive therapy (which seemed to oppose their results).

Many studies provide evidence that the lowering of BRS is what precedes and causes hypertension. In 2019, Chen et al ran an experiment where Wistar Kyoto rats ($n = 4$–8) were fed 10% fructose water for a week, to determine the mechanism behind the blood pressure elevation following fructose intake.[23] One of the main findings was that the high intake of fructose would reduce the nitric oxide levels in the NTS and reduce BRS within a week. This data, along with the increase in blood pressure, suggested that the baroreflex dysfunction (due to the fructose intake) stimulated sympathetic nerve activity, inducing the development of high blood pressure. However, limitations included the small sample size, and blood pressure having been measured during consciousness while BRS was measured when under anesthetic.

A 2019 study conducted by Matthews et al was also very indicative of deterioration of BRS preceding blood pressure elevation.[24] The study attempted to find out if young healthy women with a family history of hypertension would have a lower BRS than other healthy women without a family history. The BRS of 12 young healthy women (mean arterial pressure 79 ± 1 mm Hg) with a family history of hypertension were compared with 13 young healthy women (mean arterial pressure 77 ± 2 mm Hg). Resting cardiovagal BRS and cardiovagal BRS during phase IV (but not phase II) of the Valsalva maneuver was lower in the group with a family history of hypertension ($p = 0.02$ and $p < 0.01$, respectively). They were able to conclude from the data that having a family history of hypertension reduced cardiovagal BRS in these young women and that low BRS may be a contributing factor to the development of hypertension. A similar study in 2010, which specifically looked at men ($n = 182$), received similar results.[25]

Finally, data on BRS being lower in patients with white-coat hypertension would support the idea of BRS declining preceding blood pressure elevation.[19] In 2006, Honzíková et al ran a study where they examined the BRS (and other components) of 24 hypertensive subjects, and 30 subjects with white-coat hypertension (while also comparing each group to a control group of age-matched healthy individuals; the control groups had double the sample size of their corresponding experimental groups).[26] When compared with their control groups, the hypertensive subjects had a BRS that was on average lower by 3.5 ms/mm Hg ($p < 0.001$), while for subjects with white-coat hypertension it was lowered by approximately 3.7 ms/mm Hg ($p < 0.01$). Since white-coat hypertension would not be enough of a source for the remodeling of arterial walls,[19] lower BRS in white-coat hypertensives is strong evidence that BRS can precede high blood pressure (although unclear if the low BRS is a cause for white-coat hypertension). A similar study conducted by Sheng et al in 2020 involved 645 subjects, 28 of whom were white-coat hypertensive.[27] However, Sheng et al's study showed that subjects with white-coat hypertension did not show any significant signs of a lower BRS ($p \geq 0.12$). Both studies had relatively smaller sample sizes (of white-coat hypertensives); therefore, not much at this point can be concluded about low BRS preceding hypertension from these studies.

Arterial Stiffness and Aging

As mentioned earlier, one of the likely explanations for the strong negative correlation between BRS and blood pressure is that the increase in arterial stiffness (due to high blood

pressure) damages/deactivates the baroreceptors. Multiple clinical studies have supported this explanation by providing results showing a negative correlation between BRS and arterial stiffness. One of these studies was conducted by Michas et al in 2012.[28] Their study aimed to evaluate the relationship between BRS (which was expressed as the α-index) and pulse wave velocity (PWV; a measurement indicating arterial stiffness). After examining 160 patients, a strong correlation was found between PWV and log(α-index) ($p = 0.019$). An increased arterial stiffness had been concluded to be significantly and independently correlated with impaired BRS in both normotensive and hypertensive patients. Another study in 2014, conducted by Tomiyama et al, aimed to examine the specific pathophysiological abnormalities of vascular function that would contribute to a lower BRS.[29] In 280 hypertensive subjects, they took measurements for the brachial-ankle PWV, radial augmentation index, brachial artery flow-mediated vasodilation, and BRS. The brachial-ankle PWV (and not the other two measurements) was found to have a significant independent relationship with BRS ($p < 0.043$). Increased stiffness of the large to middle-sized arteries, as opposed to abnormal central hemodynamics or endothelial dysfunction, appeared to have contributed to abnormal baroreflex regulation in patients with hypertension. Similar results have been found in other studies,[30] including studies with chronic hemodialysis patients[31] and with subjects undergoing stress tests.[32]

Just as with BRS deterioration, arterial stiffness has been shown to increase both with age and blood pressure. A 2002 longitudinal study run by Benetos et al examined the aortic stiffness of 483 patients over 6 years, 187 of which were hypertensive.[33] Age was found to be a strong determinant of PWV in both normotensives and hypertensives ($p < 0.0001$). Additionally, when adjusted for age, sex, and initial PWV values, the annual progression of PWV in treated hypertensives was significantly higher than in normotensives (171 ± 20 vs. 66 ± 16 mm/s per year, $p = 0.0003$). Another longitudinal study in 2013 conducted by AlGhatrif et al had similar results, with PWV correlating with age and blood pressure (however, in men more than women).[34] A 2009 review compiled by Cecelja and Chowienczyk researched previous studies addressing PWV's relationship with age and blood pressure.[35] They came across 77 articles that addressed their topic and found that age and blood pressure were consistently independently associated with carotid-femoral PWV (91 and 90% of studies, respectively).

As mentioned, there had been a debate regarding which of the two, between BRS and hypertension, was the cause of their very strong correlation, with a conclusion that it was really both. Research regarding arterial stiffening and hypertension, and determining which is the cause of the other, very much resembles the mentioned debate on BRS and hypertension. For example, in a 2012 longitudinal study, Kaess et al aimed to examine temporal relationships among vascular stiffness, central hemodynamics, microvascular function, and blood pressure progression in 1,759 subjects.[36] Included in the results were that a higher aortic stiffness was associated with a higher risk of incident hypertension ($p = 0.006$), but that initial blood pressure was not independently associated with a risk of progressive aortic stiffening. The study's results led to the conclusion that vascular stiffness was what caused hypertension, and not the other way around. On the other hand, other studies have shown that heightened blood pressure is what may lead to arterial stiffening. For example, a 2012 experiment run by Fridez et al induced hypertension in 24 Wistar rats, with mean blood pressure rising from 92 ± 2 to 145 ± 4 mm Hg.[37] Within 8 days of aortic occlusion, an $18 \pm 4\%$ increase in arterial stiffness was observed, and $40 \pm 2\%$ at 56 days after. Many other studies also bring evidence for arterial stiffness being what causes hypertension,[38–43] and vice versa.[35,44–49] Using all this information, a likely conclusion would describe that arterial stiffness and hypertension can be causes of each other, with variance in which will precede the other. Likewise, Humphrey et al in a 2016 review described that wall biomechanics and hemodynamics reveal an "insidious positive feedback loop" that may render it irrelevant whether hypertension causes or is caused by central arterial stiffening.[50]

Chemoreceptors and Age

There has been much debate over the recent decades about the effects of age on chemoreceptors. Many studies have provided evidence that chemoreflex either declines, stays the same, or even increases with age. For example, a study conducted in 2004 by Pokorski et al looked at the effect of age on the morphology and function of the carotid body.[51] Morphology was studied in rats of different ages, and the function in hypoxic ventilatory responses of human females of different ages. While morphological results showed deterioration with age, ventilatory responses in humans showed sustained function. One of the multiple explanations included in the discussion explained the possibility that chemoreflex improves with increasing age. However, Pokorski et al's study is limited in that they only measured the ventilatory responses. This limitation is also found within many other studies with results that have supported older age correlating with lower ventilatory responses to hypoxia and hypercapnia[52–54] and results supporting lack of correlation between age and ventilatory response to hypoxia[54] or hypercapnia.[55,56] Since there is great reason to believe that respiratory muscles weaken with age,[57] a decrease in ventilatory response should not be attributed with certainty to a declining chemoreflex sensitivity. It is therefore much more effective to look at studies that have measured either occlusion pressures or cardiac responses to hypoxia or hypercapnia.

A 2003 study conducted by Pokorski et al aimed to determine the potential adverse effects of age on the hypoxic ventilatory response.[58] They did this by comparing the response of 19 healthy women of mean age 71 ± 1.3 (standard error) years with 16 healthy women in their twenties. Mouth occlusion pressure (P0.1), an index of inspiratory neuromuscular drive, was used to evaluate the ventilatory response. P0.1 was graphed against SaO_2 to determine the hypoxic response, with the slopes being 0.014 ± 0.002 and

0.012 ± 0.002 kPa/%SaO_2 for the younger and older groups, respectively. There was no significant difference between the mean value of the two age groups' two slopes. To determine neuromuscular output, P0.1 was graphed against VT/TI (VT = tidal volume; TI = inspiratory time), and no significant differences were found between the two groups. The study concluded that there was no evidence for an appreciable decline of neuromuscular output during acute progressive hypoxia in healthy elderly women and that their respiration seemed well suited to compensate for the physiological lowering of lung volumes with age, possibly implying an improvement of chemoreflex function.

Another study, conducted by Paleczny et al in 2014, sought to characterize reflex responses from peripheral and central chemoreceptors in different age groups of healthy men and to assess whether there is any relationship between ventilatory and hemodynamic responses from chemoreceptors, relating to age.[59] Sixty-seven healthy men were divided into two groups, < 50 years ($n = 38$, mean age: 32 ± 10 years) and $\geq$ 50 years ($n = 29$, mean age: 61 ± 8 years). Respiratory, heart rate, and blood pressure responses were calculated during the transient hypoxia method, and central chemoreflex sensitivity was assessed by the rebreathing method, looking at the respiratory response. Results provided no difference in respiratory responses from central and peripheral chemoreceptors between the two groups, corresponding to Pokorski et al's 2004 study. However, significant differences were found in hemodynamic responses from peripheral chemoreceptors. The older group reacted to transient hypoxia with a lower heart rate acceleration (which was actually found to be related more to reduced BRS), but a greater increase in systolic blood pressure than the younger group.

A similar study, but with contrasting results, was conducted by García-Río et al in 2007.[60] They aimed to compare the central inspiratory drive response between different age groups of healthy subjects. In 67 subjects, mouth occlusion pressure responses to hyperoxic progressive hypercapnia and isocapnic progressive hypoxia were evaluated. The elderly subjects had lower P0.1 responses to hypoxia (0.017 ± 0.006 vs. 0.031 ± 0.008 kPa/%, $p < 0.001$) and hypercapnia (0.042 ± 0.018 vs. 0.051 ± 0.030 kPa/mm Hg, $p = 0.047$) when compared with the younger group. It was also noteworthy that hypoxic sensitivity gradually decreased until the age of 75, and then remained unchanged.

Finally, a 2012 study by Lhuissier et al intended to learn how aging modifies ventilatory and cardiac responses to hypoxia.[61] The study assessed the physiological responses (desaturation and ventilatory and cardiac responses at rest and exercise) to hypoxia through a cross-sectional 20-year study including 4,675 subjects (men and women, ages 14–85) and a longitudinal study of 30 subjects (explored at a mean 10.4-year interval). The data had shown that in men, the ventilatory response had increased ($p < 0.002$) with increasing age, while desaturation was less noticeable ($p < 0.001$). Like Paleczny et al's study, cardiac response to hypoxia decreased with increasing age ($p < 0.001$) in both sexes. Similar results were found in the longitudinal study.

Chemoreceptors and Hypertension

As opposed to baroreceptors, there has not been much research on the effects of deteriorating chemoreflex sensitivity on blood pressure (which is reasonable, as baroreceptors play a relatively larger role when controlling blood pressure). However, several studies have focused on the surgical removal of the carotid body/chemoreceptors followed by decreasing blood pressure.

A 2013 study run by Ribeiro et al investigated the role of the peripheral chemoreflex in the pathogenesis of metabolic and hemodynamic diseases, hypothesizing that their activity is increased in insulin resistance and hypertension in animal models.[62] Additionally, chronic carotid sinus nerve bilateral resections were performed, testing if preventing the carotid body (peripheral chemoreflex) from being overactivated would avoid the development of insulin resistance and hypertension. Diet-induced insulin-resistant and hypertensive Wistar rats were used, and the resection was performed on them. The 37.25% increase in mean arterial pressure that occurred in the rats after being placed on their diets was totally prevented by the carotid sinus nerve resection (after comparing the mean arterial pressure of 7 rats postresection with 10 of the rats without any resection; $p < 0.001$).

A very similar study conducted in 2016 by Pijacka et al performed the same resection in Goldblatt hypertensive Wistar rats (two kidneys, one clip).[63] Nine of the rats underwent the surgery, and nine others underwent a sham surgery (all after 5 weeks after the renal artery clipping), and they were all compared with five controls. Hypertensive rats showed a higher blood pressure by approximately 149 mm Hg ($p < 0.001$). The removal of the carotid body had reduced the arterial blood pressure of the originally hypertensive rats, also preventing further increase in blood pressure which was seen in the rats with the sham carotid resection; by the third week, the between-group difference was 14 ± 2 mm Hg ($p < 0.01$).

In 2014, Sinski et al conducted a study that sought to apply these findings to human chemoreceptors.[64] The study compared the effect of acute hyperoxia on hemodynamic parameters between hypertensive ($n = 12$) and normotensive ($n = 11$) male subjects. By oversupplying the subjects with oxygen, the chemoreceptors would temporarily be shut off, comparable to a temporary removal. After 30 seconds of 100% oxygen from a non-rebreather mask, hypertensives (but not normotensives) experienced a significant reduction in systolic, diastolic, and mean blood pressure. However, this effect was gone after 20 more minutes of exposure to hyperoxia, which was likely due to vasoconstriction directly induced by hypoxia. These studies have provided evidence of the benefit of additional future research on chemoreflex as a possibility to improve blood pressure in hypertensives.

Conclusion

In conclusion, there has already been an overwhelming amount of research providing evidence for the negative correlation between age and BRS.[58] However, the relationship between age and chemoreflex sensitivity is still very

much up for debate, with research either supporting evidence of a positive, negative, or lack of correlation between the two. There is also a great amount of research showing a negative correlation between hypertension and BRS. While several studies had provided evidence that high blood pressure was the cause of a lower BRS, derivations were made from other studies showing that a low BRS may also bring about hypertension, making it a two-way street. There has not been clarity yet about which is the more common cause, and by how much. Regarding chemoreflex and its relationship with hypertension, most research has shown examples of surgical removal of the chemoreceptors in animals, and its effects in lowering blood pressure. Noninvasive experiments which deactivate the chemoreceptors in human bodies, such as in Sinski et al's study, show the potential of additional future research into the carotid bodies to lower blood pressure.

Conflict of Interest
None declared.

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