Potential Benefits of Caffeine Alone or in Combination with Nitrate Supplementation in Blood Pressure Control in the Elderly

Abstract

The elderly population is characterized by its susceptibility in their cardiovascular system and thus likely to developing cardiovascular diseases as well as related events associated to the aging process (e.g. to psychiatric disorders). The elderly population consumes high amounts of substances containing caffeine. If on one hand the chronic consumption of caffeine-containing substances (in particular coffee) may be beneficial, on the other hand acute consumption might be harmful to the cardiovascular system (e.g. by increased blood pressure). Acute caffeine consumption also promotes other benefits to elderly population such as to increase physical performance and aids in the treatment of symptoms related to psychiatric disorders. A potential substance that could inhibit the acute effects of caffeine on the cardiovascular system is inorganic dietary nitrate. Inorganic dietary nitrate supplementation has been show to be an effective hypertensive substance (through nitric oxide production via the nitrate-nitrite-no pathway) with no apparent adverse effects. The aim of this review was to highlight, with data published in the literature, the effects of caffeine and dietary nitrate, isolated and in association on blood pressure modulation in the elderly population. Whilst they have been studied independently in the elderly, they have only been studied in combination in young healthy adults.

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Diana Madureira[1], Jeferson Oliveira Santana[1], Elias de Franca[2], Cesar Augustus de Sousa Zocoler[1] and Erico Chagas Caperuto[1,2]*

[1]Department of Physical Education and Aging Sciences Post Grad Programs, Sao Judas Tadeu University, Brazil

[2]Department of Centro de Ciências Biológicas e da Saúde, Mackenzie Presbiterian University, Brazil

***Corresponding author:** Erico Chagas Caperuto, Department of Physical Education and Aging Sciences Post Grad Programs, Sao Judas Tadeu University, Rua da Consolacao, Brazil, Email: ericocaperuto@gmail.com

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Introduction

The Aging process promotes anatomic and functional changes in several systems of the organism [1]. The mainly changes that happen in the cardiovascular system are cardiomyocytes hypertrophy with reduction in their number, decrease in the sensitivity of beta adrenergic stimuli, catecholamine's and maximum cardiac output, arterial wall thickness and increase in the sub endothelial collagen, in the inflammatory markers, in the pulse wave and peripheral vascular resistance [2]. These changes result in an increase in the blood pressure (BP) in the elderly population, a scenario that might progress to hypertension and other possible complications that might come from it, such as stroke, heart ischemia and arterial diseases among others [3]. Those conditions might also be worsened by deleterious nutritional habits.

Caffeine is a fast absorbed stimulant substance with action in the whole body that reaches its peak in 30 to 90 minutes. It has been well established in the literature that the consumption of 3 to 6mg/kg of caffeine is needed to obtain an Ergogenic effect [4] however; it might increase BP and reduce blood flow [5]. In young adults, caffeine acute supplementation (200mg) when combined with exercise can decrease (14-22%) myocardial blood flow [6,7]; moreover, 300mg when combined with exercise can lead to a reduction of blood flow and vascular conductance in the arm by ~50% and increase angiotensin II (ANG II) by ~44% [8].

These caffeine hypertensive effects seem to last several hours after physical exercise [9]. Blood flow decrease do not seems to occur when individuals are at rest, it is speculated that the hemodynamic effects of caffeine during exercise are due to the fact that caffeine antagonizes the vasodilator effects of physical activity (i.e. it inhibits the adenosine receptors) [10]. The afore mentioned data suggests us that when individuals engage in physical activity after caffeine intake, they are exposed to a greater risk of suffering a cardiovascular event (e.g, myocardial ischemia or cardiac arrhythmia) compared to the situation of non-physical activity or physical activity without caffeine intake [10].

Other caffeine effects are analgesic promotion, decrease in pain sensitivity; thermo genesis increase and fatigue delay during physical exercise [4]. Caffeine has many effects on central nervous system, such as catecholamine release, focus, and mood, state of alert, reaction time and memory improvement [4]. In particular, these effects make caffeine a powerful cryogenic and treatment aid in several diseases related to aging such as Parkinson and Alzheimer's diseases, depression, cognitive failure, etc. [11,12].

Caffeine can be found in coffee, tea and chocolate among other foods/drinks, with the amount of caffeine being different between them. It is one of the most consumed substances by elderly population and that might be negative to the cardiovascular function when consumed in excess [13]. More than a habit, caffeine consumption has positive effects on several aspects of the elderly day to day activities [14], reinforcing this routine. On the other hand, nitrate supplementation is an effective strategy to increase nitric oxide (NO) availability in the body. NO is considered a potent vasodilator and it has influence in different metabolic processes of the body, thus the importance of maintaining adequate levels

of this substance in the body. Some of the actions of NO are to regulate BP and blood flow, to influence muscle contractility, cellular respiration process, calcium and glucose metabolism [15,16].

Interestingly, several complications such as atherosclerosis, stroke and especially hypertension, are associated with reduced NO bioavailability, or even a deficiency in its production [17,18]. Nitrate is available for consumption in two main forms, as organic nitrate or inorganic nitrate. Inorganic nitrate can be found in several natural sources and it is considered healthy and therefore has no side effects presented so far [15-20]. Inorganic nitrate (instead of organic nitrate) has been chosen as the most used option for nitrate supplementation due to its salivary regulation (which prevents NO spurt) [20]. Inorganic nitrate it is present, mainly, in vegetables, and is encountered in larger concentration in arugula, spinach, lettuce, celery and beetroot [20].

The inorganic nitrate pharmacokinetics that results in NO bioavailability starts in the mouth, where anaerobic bacteria (located in the tongue) transforms nitrate in nitrite. After this modification, nitrite arrives in the stomach, where it is converted to NO and is absorbed; it enters the bloodstream and is distributed throughout the body [21].

Once in its action site, NO stimulates cyclic guano sine monophosphate (cGMP) production which in high concentration reduces calcium entrance in the sarcolemma and reduces calcium release of its storage sites promoting vasodilatation [22]. Furthermore, the increase of NO production reduces the Ang II activity in the renal tubules (inhibiting renal vasoconstriction), preventing an increase in systemic BP [23].

NO action peak occurs, on average, between two to three hours after inorganic nitrate consumption [24,25]. Inorganic nitrate consumption may promote a 2.5 to 6.4mmHg decrease in systolic BP and a 0.4 to 3.0mmHg decrease in diastolic BP [26]. Inorganic nitrate peak effect on BP occurs 2.5-3 hours following ingestion (coinciding with nitrite plasma levels) and its half-life is between 5 and 8 h [20].

Although there are few studies which approach inorganic nitrate supplementation for the elderly population, the results are positive regarding BP control (or its decrease), using dietary sources of nitrate.

Therefore, the aim of this review was to discuss, with data published in the literature, the effects of caffeine and inorganic dietary nitrate, isolated and in association on BP modulation in the elderly population.

Methods

A systematic review was conducted by 4 independent researchers on two different electronic data bases. We used articles from 2006-2016, searched on PubMed and EBSCO (Figure 1). Fluxogram search of caffeine and inorganic nitrate combination in elderly blood pressure. The key words used were caffeine (caffeine OR coffee OR 1, 3, 7-trimethylxanthine), nitrate (nitrate OR beet OR beta vulgaris OR lettuce OR spinach), blood pressure (blood pressure OR hypotension OR hypertension), and elderly (elderly OR aged OR aging) combined at least in pairs. References found were all closely examined to ensure adherence of the article to the subject. We included articles with all key words in the title (or in the abstract) which approached the substances combination on BP behavior, in the elderly. Later we also included articles that would approach caffeine or inorganic nitrate alone on BP behavior, in the elderly. We excluded articles that addressed caffeine or inorganic nitrate with other supplements and articles that considered other circumstances instead of BP control (Figure 2). Fluxogram searches of isolated caffeine and inorganic nitrate supplementation in elderly blood pressure.

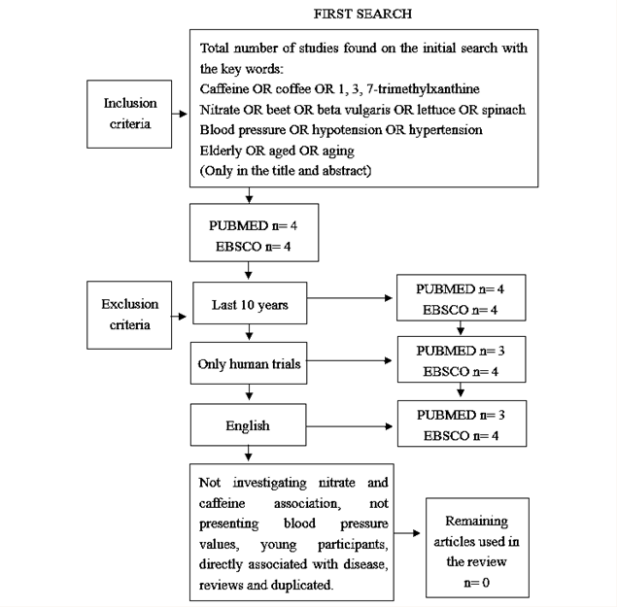

Figure 1: Fluxogram search of caffeine and inorganic nitrate combination in elderly blood pressure.

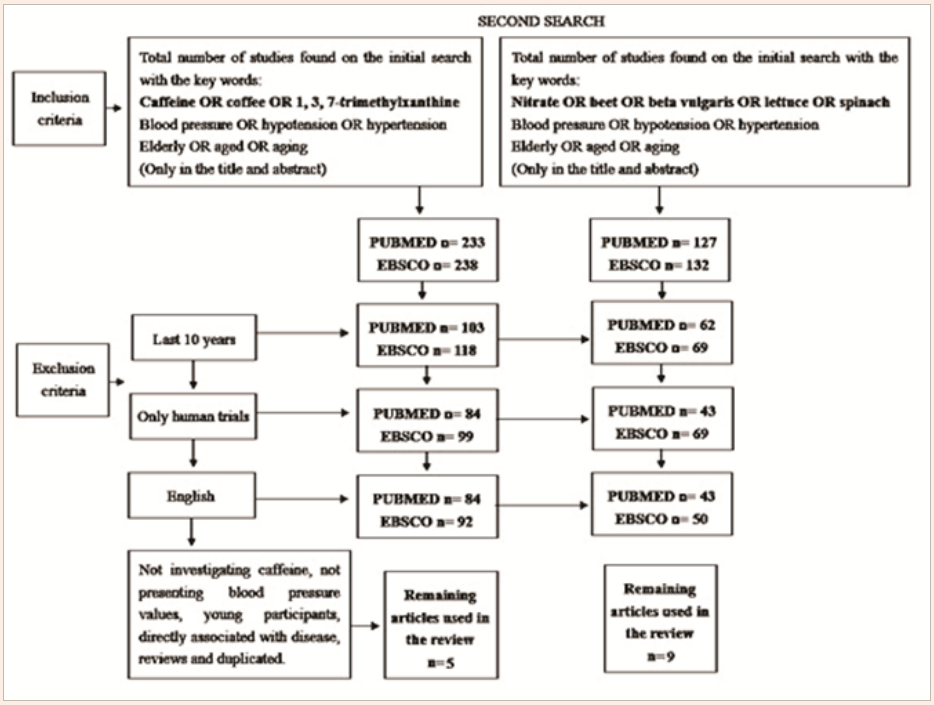

Figure 2: Fluxogram searches of isolated caffeine and inorganic nitrate supplementation in elderly blood pressure.

Results

When we used all the key words in combination, we retrieved 0 articles from both databases (Figure 1). There seems to be no papers, until now, that analyzed both substances in combination and its effects on BP behavior in the elderly.

The search with the key words caffeine or nitrate alone with blood pressure and elderly was more fruitful, we found 233 articles with caffeine, blood pressure and elderly as key words and 127 articles with nitrate, blood pressure and elderly as key words (and all related terms as described above) that were further processed to the end result of 5 and 9 articles, respectively (Figure 2) a summary of all articles used in the review are presented in (Tables 1&2).

Acute caffeine supplementation might increase BP [34]. However, chronic coffee consumption presented conflicting date, while some studies [31-33] associate chronic coffee consumption with lower risk of CHD development, one study [28] presented adage-related increase in systolic BP and pulse pressure increased at high levels of coffee consumption (Table 2). Of nine studies with inorganic nitrate supplementation, only one study [45] did not showed decrease in BP after inorganic nitrate supplementation/ feeding condition (Table 1).

Table 1: Studies resulting from words combination (*i.e.* nitrate, blood pressure and elderly) and its related terms.

Study	Participants	Objective	Methods	Results	Conclusion
Kapil et al. [40]	Hypertensive patients aged 18-85 years. (n=64)	To assess whether dietary nitrate might provide sustained blood pressure (BP) lowering in patients with hypertension.	4-weeks daily supplementation of Nitrate (n=34): 250mL beetroot (BR) juice (~6.4mmol); Placebo (n=34): 250mL nitrate-depleted BR juice (~0.007mmol).	Reductions in BP. Clinic BP was reduces by 7.7- 2.4 mmHg; Twenty-four-hour ambulatory BP was reduced by 7.7- 5.2 mmHg; and Home BP was reduced by 8.1-3.8 mmHg.	Dietary nitrate provision to hypertensive patients provides robust BP lowering that is dependent on the conversion of nitrate to nitrite and thence NO.

Jajja et al. [41]	Older, overweight subjects mean age 62.0±1.4 years. (n=21)	To assess whether oral supplementation of BR juice concentrate might decrease BP in overweight older participants and observe if this effects would be sustained after a 1-week interruption of the supplementation.	For 3 weeks, participants were randomized either toBR juice concentrate or blackcurrant juice group, with a 1-week post supplementation phase.	BR juice supplementation was not associated with significant changes in resting clinic BP or 24-hour ABPM. Conversely, it reduced daily systolic BP after 3 weeks (-7.3 ± 5.9 mmHg). The effect was not maintained after the interruption of the supplementation.	In overweight older subjects, BR juice concentrate supplementation was associated with beneficial effects on daily systolic BP, although the effects were not significant when measured by 24-hour ABPM or resting clinic BP.
Liu et al. [42]	Participants aged 38-69 years. (n=26)	To assess the acute effects of a nitrate-rich meal containing spinach on arterial stiffness and BP in healthy men and women.	Two acute energy-matched (2000 kJ) meals, high nitrate meal (220 mg of nitrate derived from spinach) or low nitrate (control).	Spinach compared with control resulted in lower pulse pressure, and systolic BP. However, post meal diastolic BP was not significantly altered by spinach relative to control.	The consumption of a nitrate-rich meal can lower systolic BP and pulse pressure and increase large artery compliance acutely in healthy men and women.
Siervo et al. [26]	254 participants with 7-30 participants/study (18- ~70yr)	Conduct a systematic review and meta-analysis of randomized clinical trials that examined the effects of inorganic nitrate and BR juice supplementation on BP	Search between 2006 and 2012 in Medline, EMBASE, and Scopus databases.	Inorganic nitrate and BR juice consumption were associated with greater changes in systolic BP [-4.4 mm Hg (95% CI: -5.9, -2.8); P < 0.001] than diastolic BP [-1.1 mm Hg (95% CI: -2.2, 0.1); P = 0.06]. There is an association between daily dose of inorganic nitrate and changes in systolic BP (P < 0.05).	Inorganic nitrate and BR juice supplementation was associated with a significant reduction in systolic BP. These findings need to be tested in long-term trials and in individuals at greater cardiovascular risk.
Kelly et al. [43]	12 healthy, older (60-70 yr) adults	Investigated whether dietary nitrate supplementation reduce resting BP and alter the physiological response to exercise in older adults.	A double-blind, randomized, crossover study composed by 3 days with either nitrate-rich concentrated BR juice (2 × 70 ml/day, ~9.6 mmol/day nitrate) or a nitrate-depleted BR juice placebo (PL; 2 × 70 ml/day, ~0.01 mmol/day nitrate).	Nitrate supplementation significantly ↑ plasma [nitrite] and ↓ resting systolic (BR: 115 ± 9 vs. PL: 120 ± 6 mmHg; P < 0.05) and diastolic (BR: 70 ± 5 vs. PL: 73 ± 5 mmHg; P <0.05) BP. Also reduced The VO_2 mean response time and the O_2 deficit.	Dietary nitrate supplementation reduced resting BP and improved V̇o2 kinetics during treadmill walking in healthy older adults. These results may have implications for the enhancement of cardiovascular health in older age.

Gilchrist et al. [45]	27 patients (18 male) with type 2 diabetes mellitus (T2DM), BP >125/85 mmHg, (at last 5 years) age 67.2 +/-4.9 years.	Determine if supplementing dietary BR juice (rich source of nitrate) will lower BP, improve endothelial function and insulin sensitivity in individuals with T2DM.	A randomized double-blind study with 2 week period of supplementation with 250 ml BR juice daily or 250 ml nitrate-depleted BR juice (placebo).	Twenty-four-hour ambulatory of systolic BP neither both macro vascular or micro vascular endothelial function and insulin sensitivity do not change.	7.5 moles of nitrate per day for 2 weeks caused an increase in plasma nitrite and nitrate concentration, but did Not lower BP; improve endothelial function or insulin sensitivity in individuals with T2DM.
Kenjale et al. [49]	8 subjects (4F; 4M; age 67 ± 13 yr) with peripheral artery disease and intermittent claudicating.	Investigate the acute effects of BR juice beverage ingestion on plasma nitrate and nitrite levels, exercise tolerance and tissue oxygenation during exercise in subjects with diagnosed peripheral artery disease.	In a randomized, open-label, crossover way, subjects underwent resting blood draws, followed by consumption of 500ml BR or PL and subsequent blood draws prior to, during, and following a maximal cardiopulmonary exercise test.	BR increased plasma nitrite after 3 h. Subjects walked 18% longer before the onset of claudicating pain and had a 17% longer peak walking time following BR vs. PL. Gastrocnemius tissue fractional O_2 extraction was lower during exercise following BR. Diastolic BP was lower in the BR group at rest and during exercise test.	NO signaling increases peripheral tissue oxygenation in areas of hypoxia and increases exercise tolerance in subject with peripheral artery disease.
Siervo et al. [51]	85 older participants (age range: 55-76 years) from four independent randomized clinical trials.	Studied the effects of high-nitrate BR juice supplementation on BP variability measured by 24-hr ambulatory BP monitoring (24-hr ABPM) in older subjects.	Meta-analysis was conducted to obtain pooled estimates of the effect size for each BP outcome. Sub-group analyses were conducted to evaluate the influence of age, BMI, gender, BP status and changes in nitrite concentrations on the effect size.	BR juice ingestion determined a significant decrease in nocturnal systolic BP variability in subjects aged less than 65 y (2.8 mmHg, -4.5 −1.0, p = 0.002) compared to the older group (≥65 y; 1.0 mmHg, -2.2 4.2, p = 0.54). A greater change in nitrite concentrations after beetroot supplementation was associated with significant differences for nocturnal mean (-3.4 mmHg, -0.6 -2.4, p = 0.02) and variability (-0.8 mmHg, −1.5 -0.06, p = 0.03) of systolic BP.	The vascular responsiveness to inorganic nitrate may be modified by mechanisms of vascular ageing influencing the reducing capacity to convert inorganic nitrate into nitrite and tissue-specific responses to dietary nitrate supplementation.

Table 2: Studies resulting from words combination (*i.e.* caffeine, blood pressure and elderly) and its related terms.

Study	Participants	Objective	Methods	Results	Conclusion
Giggey et al. [28]	Participants from the Baltimore Longitudinal Study of Aging (BLSA) (865 women and 1,577 men; n=2,442)	To examined longitudinal relations of habitual coffee use to resting BP and pulse pressure.	Coffee consumption was used to predict resting systolic and diastolic BP and pulse pressure using longitudinal mixed-effects regression models (every 2-3 years). Age was examined as possible effect modifiers.	In men, were identified a significant three-way interaction among coffee intake (nonlinear), baseline age, and length of follow-up for systolic BP (SBP) and pulse pressure. A significant interaction of coffee intake and BMI (nonlinear) was also noted for SBP in men. There were no significant relations of coffee intake to BP or pulse pressure in women.	Greater coffee intake in men was associated with steeper age-related increases in systolic BP and pulse pressure, particularly beyond 70 years of age and in overweight to obese men.
Greenberg et al. [31]	Normotensive subjects aged 65.4 to 96.6 years (n=1,354)	To test the association between caffeinated coffeeconsumption and heart disease (CHD) morbidity and mortality, in elderly s ubjects without moderate to severe hypertension.	A 10.1 years of follow-up, in which cardiovascular risk factors and health behaviors were carefully documented.	A significant negative association between caffeinated coffee consumption and CHD mortality was observed for subjects with systolic blood pressure (BP) <160mmHg and diastolic BP <100mmHg. The decrease in risk of CHD mortality for any caffeinated coffee appeared to be caused primarily by an inverse prospective relation between caffeinated coffee consumption and the development or progression of heart valve disease.	Caffeinated coffee consumption was associated with lower risk of CHD mortality and heart valve disease development or progression in older Framingham subjects without moderate to severe hypertension.
Uiterwaal et al. [33]	2,985 men and 3,383 women	To assess whether coffee intake is associated with the incidence of hypertension.	A 11 year follow up, in which baseline coffee intake was ascertained with questionnaires and BP were measured at baseline visit and follow-up visits after 6 and 11 y.	Coffee abstainers at baseline had a lower risk of hypertension than did those with a coffee intake of >0-3cups/d. Women who drank >6 cups/d had a lower risk than did women who drank >0-3 cups/d. Subjects aged ≥39 y at baseline had 0.35 mmHg lower SBP per cup intake/d than did those aged <39 y at baseline.	Coffee abstinence is associated with a lower hypertension risk than is low coffee consumption. An inverse U-shaped relation between coffee intake and r isk of hypertension was observed in the women.
Hino et al. [32]	Japanese aged over 40 years. (785 men and 1,117 women; n=1902)	To examined the relationship between metabolic syndrome and the consumption of coffee or green tea.	Several components of metabolic syndrome (such as BP) were measured. Eating and drinking patterns were evaluated by a food frequency questionnaire	BP was significantly and inversely related to coffee but not green tea consumption. The larger was the number of components of metabolic syndrome; the lower was the level of coffee consumption. In addition, there was a high frequency of metabolic syndrome in small coffee drinkers	Coffee but not green tea consumption was inversely associated with metabolic syndrome.
Farag et al. [34]	165 healthy men and women (35 to 64 yrs)	To examined the effect of caffeine on BP in postmenopausal women and old man (50-64 yrs) vs. premenopausal women and young men (35-49 yrs).	Caffeine or placebo maintenance (80 mg, 3x/day for 6 days) followed by testing of response challenge dose (250 mg) of caffeine or placebo.	Caffeine challenge dose resulted in a significant increase in systolic (4 ± .6 mmHg, $p < 0.01$) and diastolic (3 ± .4 mmHg, p mmHg.4sBPin healthy, normotensive, young and older men and women.	This finding warrants the consideration of caffeine in the lifestyle interventions recommended for BP control across the age span.

Discussion

We searched for a combination of all key words with no success, both databases retrieved zero (0) results. It seems that the idea of studying caffeine (in order to improve performance during physical exercise) and inorganic nitrate (to prevent BP to increase in an excessive manner) combined is an idea for future studies. However, we could find some studies that might be useful for us to speculate how these substances behave, used separately, and how they affect the elderly BP. There is no literature consensus about the effects of caffeine consumption on BP increase. Turley et al. [27] report that BP increase can happen from the consumption of approximately 5mg/kg of caffeine (Table 3).

Table 3: Effects of caffeine and Inorganic nitrate consumption in the organism.

	Caffeine	Nitrate
Adenosine Activity	Inhibition [4, 5, 11]	Stimulus [21]
Angiotensin II Production	Increase [5, 10]	Decrease [47]
Guanosine Monophosfate Cycle	Block	Stimulus [18, 23, 47]
Sarcoplasmatic Reticulum Calcium Release	Stimulus [5,10]	Inhibition [19]
Sarcolemma Calcium Concentration	Increase [5]	Decrease [21]
Nitric Oxide Synthase	Block [46]	NO Backup [47]

When we look to it from the elderly point of view, it seems that caffeine consumption is acutely associated with an increase in BP and pulse pressure related to increasing age. That is especially true for overweight and over 70 years subjects [28]. In contrast, some authors have shown that long-term coffee consumption may be beneficial in cardiovascular and metabolic functions [29,30].

However, it seems that chronic caffeine consumption (in the coffee form) seems to be associated with lower cardiovascular disease risk and metabolic syndrome [31,32], although Uiterwaal et al. [33] found an association with hypertension risk and abstinence of coffee consumption. Farragut et al. [34] demonstrate that acutely caffeine supplementation (250mg) increased BP independently of age, gender or hormonal status, even in caffeine chronic consumers (i.e., 80mg/day). These effects can be attributed to two factors.

The first one is the vasoconstriction which occurs due to an increase in angiotensin II (ANG II) production and noradrenalin release [10]. Adenosine has an antagonist effect to caffeine, promoting inhibitory effects in the organism. As both these substances compete for the same receptors (situated in brain and blood vessels) the consumption of sufficient amounts of caffeine can prevent the receptors of being stimulated by adenosine. Also, one of the adenosine functions is the inhibition of neurotransmitters release, such as noradrenalin. Because caffeine acts directly in adenosine receptors it ends up facilitating this neurotransmitters release [35,36]. The second one is the vasoconstriction, which happens due to both the block of cyclic guano sine monophosphate (cGMP) and the decrease in adenosine action. The cGMP activity stimulates calcium reabsorption, when it is inhibited it causes the endothelium cells to be hyperpolarized, due to high concentration of calcium in cellular cytosol. Thus, endothelium cells become unable to relax and to promote vasodilatation [10].

Together these data indicate that it seems to occur a hormesis phenomenon on BPdueto chronic caffeine consumption, as well as it occurs with physical exercise [37]. Recent human [15-38] and animal [23-39] evidences show that acute inorganic nitrate ingestion promotes vasodilatation and consequently decreases BP in both normotensive and hypertensive conditions, as well as it might prevent kidney injuries in these conditions [39]. A meta-analysis study by Servo et al. [26] (including both young and elderly population) showed that inorganic nitrate supplementation decreased arterial BP in an average of -4.4mmHg, meanwhile diastolic BP decreased -1.1mmHg and this alterations are associated with a daily dose of inorganic nitrate ingestion.

Specifically in the elderly, Kapil et al. [40] found significant BP decreases with 4 weeks of beetroot juice consumption (with ~6.4mmol of nitrate) on hypertensive patients (18-65 years). Another study with elderly people (average 62 years) reported that concentrated beetroot juice (for 4-weeks, with 6.4mmol of nitrate) reduced significantly daily BP Jaja A et al. [41]. In healthy men and women (38-69 years), Liu et al. [42] showed a lower systolic BP, pulse pressure and increased large artery compliance, after an acute meal rich in inorganic nitrate (220 mg). In addition, a double-blind, randomized, crossover study composed by 3 days with either nitrate-rich concentrated (~9.6 mmol/day) beetroot juice also showed a decrease in both diastolic and systolic BP, in elderly (60-70 yr) [43].

In a study with mice [44] it has been showed that inorganic nitrate supplementation (8 to 10 wk) improves several aspects of metabolic syndrome (such as insulin sensitivity, hypertension and endothelial dysfunction). This study is important, because endothelial dysfunction is commonly present in hypertensive elderly patients. Interestingly, in T2DM (type 2 diabetes mellitus) elderly patients, Gilchrist et al. [45] did not observed any change in both diastolic and systolic BP after 2 week of beetroot juice supplementation (with 7.5 moles of nitrate per day) neither improvements in endothelial function or insulin sensitivity Chang J et al. [46]. Further research is needed, because evaluated patients who were making drug use (to control co morbidities associated to T2DM), which might affect vascular function and them the response to inorganic nitrate. Gilchrist et al. assessed neither plasma nitrite nor NO, this is necessary because NO response to inorganic nitrate supplementation varies widely between health and unhealthy elderly Lundberg JO et al. [47].

A recent meta-analysis Larsen FJ et al. [48] evaluated data of beetroot juice supplementation effect on 24-hr ABPM (ambulatory blood pressure monitoring) in older subjects, it was concluded that nitrite concentrations, followed by inorganic nitrate ingestion, works as a potential factor influencing the association between inorganic nitrate and vascular responses. So, oral micro biota, gastric redo environment, oxygen tension and pH in the peripheral circulation or reeducates enzymes efficiency (factors that influence the conversion of inorganic nitrate to

nitrite)need to be investigated in the elderly using inorganic nitrate supplementation to control BP levels Kenjale AA et al. [49].

In a study with mousse and rats Lane et al. [50] it was verified that caffeine consumption inhibits NO synthesis (blocking NO syntheses) inducing cerebral artery constriction. Despite these opposite actions NO production from inorganic nitrate supplementation is an independent pathway of NO syntheses [47], i.e., acts as a "backup" (preventing NO decrease) if a deficiency in the NO production occurs. Interestingly, caffeine with NO availability works as a protective combination during ethanol induced cerebral artery constriction [46]. Analyzing these two substances from the literature results we can assume that acute inorganic nitrate or inorganic nitrate rich meals consumption can decrease BP enough to modulate caffeine's impact on the elderly BP Siervo M et al. [51] (Table 3) shows that inorganic nitrate vascular effects are contrary to those promoted by caffeine consumption. In young subjects, inorganic nitrate consumption has been show to improve mitochondrial efficiency [48] which is related to its cryogenic potential. This results also true to elderly subjects [43-49]. These data indicates cryogenic potential (beyond cardiovascular health) of this substance to the elderly population [52,53].

Few studies can be found in the literature related to caffeine and inorganic nitrate association. These studies had the primary objective to verify caffeine-nitrate association effects in exercise performance and none of them used elderly subjects. Glaister et al. [25] offered a 7.3mmol of inorganic nitrate and 5mg/kg of caffeine to well-trained cyclists and observed an increase on their performance. However, due to caffeine group and caffeine plus inorganic nitrate group results similarity, the authors assigned this increase exclusively due to caffeine action. Lane et al. [50] conducted a study with cyclists, but with a different dosage. In this study, they offered a single dosage of 8.4 mmol of inorganic nitrate and two dosages of 1.5mg/kg of caffeine, totalizing 3mg/kg of caffeine. Similarly to the study of Glister et al. [25], the results between caffeine group and caffeine plus nitrate group were similar, so the authors concluded that inorganic nitrate has no cryogenic effects when associated with caffeine. Handizlik & Gleeson [21], on the other hand, presented benefits from caffeine/nitrate association. In their study, they offered 8mmol of inorganic nitrate and 5mg/kg of caffeine to well-trained cyclists and the results were positive. VO_2 significantly increased in the caffeine-nitrate group, compared to both substances, when consumed isolated.

These results present a general idea from caffeine and nitrate associated effects, although the extrapolation of these results to the elderly population has to be done carefully since the mentioned studies were proposed to investigate only performance in young individuals. Caffeine is a well-known cryogenic substance and a potential substance to help in the treatment of several diseases related to aging. On the other hand, elderly usually have high BP and acute caffeine ingestion might increase it even more (mainly during the physical exercise), whereas inorganic nitrate consumption might be a helpful tool (working concomitantly) to maintain the cryogenic properties of caffeine and improve exercise performance for the elderly without the side effects on BP.

Conclusion

We can conclude that acute caffeine ingestion promotes BP increase in the elderly; however, chronic consumption seems to promote benefic adaptations on BP. On the other hand acute inorganic nitrate ingestion promotes BP decreases in this population. Although adult studies analyzing caffeine, inorganic nitrate and exercise suggest a potential healthy synergic association especially to the elderly, new studies are needed to verify this suggestion.

These new studies should investigate further its effects on cardiovascular health and physical fitness with special attention to the amount and nature (meal, capsules, and drinks) of the substances consumed and to the metabolic situations (at rest or during exercise) where they are used.

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