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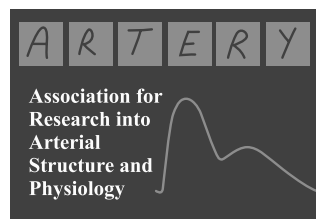
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Charalambos Vlachopoulos, Nikolaos Alexopoulos, Christodoulos Stefanadis

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Lifestyle modification and arterial stiffness and wave reflections: A more natural way to prolong arterial health

Charalambos Vlachopoulos*, Nikolaos Alexopoulos, Christodoulos Stefanadis

Hypertension and Peripheral Vessels Unit, 1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

KEYWORDS

lifestyle modification;
arterial stiffness;
wave reflection

Summary This review deals with the effect of several components of the broad term "lifestyle" on arterial stiffness and wave reflections. Caffeine and coffee have an unfavourable effect on aortic stiffness and wave reflections both on an acute and on a chronic basis. Acute consumption of tea, which contains not only a great amount of flavonoids but also caffeine, stiffens the arteries less than its caffeine content. Dark chocolate, also rich in flavonoids, has a beneficial acute effect on wave reflections, while its habitual consumption appears to have a beneficial effect both on aortic stiffness and wave reflections. Alcohol consumption has a J- or U-shaped effect on arterial stiffness and wave reflections; moderate consumption is beneficial, while high consumption may be deleterious. Salt restriction results in a rapid amelioration of arterial elastic properties. Smoking has been extensively associated with a deterioration of arterial stiffness and wave reflections both on an acute and on a chronic basis. Obesity (especially central) is generally associated with impaired arterial elastic properties, and weight loss is accompanied with improvement in arterial stiffness. Aerobic exercise is beneficial to arterial function, while resistance exercise has the opposite results. Data suggest that acute mental stress has a prolonged unfavorable effect on aortic stiffness and wave reflections.

Lifestyle has a significant, and increasingly recognised, impact on cardiovascular risk. An important part of this impact may be mediated through its effect on arterial stiffness and wave reflections given their important pathophysiological and prognostic role.

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1. General considerations

The term "lifestyle" is a rather broad one with loose, continuously expanding boundaries within which they fit processes inherent to our existence, such as diet and physical activity, acquired habits (usually bad, such as smoking) and conditions related to our psychological

attitude towards life and its stimuli, such as mental stress. The importance of efforts oriented towards the exploration of the link between lifestyle and arterial function is based on two axes. First, on the growing understanding that lifestyle has a major impact on cardiovascular diseases and that its modification may reduce cardiovascular risk in a non-pharmacological, more "natural" way, a concept which continuously gains supporters. Secondly, given the important pathophysiological and prognostic role of arterial stiffness and wave reflections, it is anticipated that a part of the reduction in cardiovascular risk is mediated through the improvement of arterial elastic

* Corresponding author. Charalambos Vlachopoulos, MD. Kerassoundos 17, Athens 11528, Greece. Tel: + 30 6972 272727; fax: +30 210 7473374. E-mail: cvlachop@otenet.gr (C. Vlachopoulos).

Table 1
Concise evaluation of available data on lifestyle and arterial function

Component of lifestyle	Rating of pathophysiological background	Rating of clinical evidence ^a	Main findings	Areas for further investigation
Diet/Nutrition				
Coffee-caffeine	3/5	3/5	Increase in AS and WR both acutely and chronically Synergistic effect with smoking	Need clarification: cut-offs of consumption, effect of other coffee ingredients
Tea	1/5	1/5	Only acute studies. Increase in WR both with black and green tea. Neutral effect on AS (green), short-lasting increase in AS (black)	Chronic effect to be investigated. Mechanisms to be elucidated (caffeine vs. flavonoids)
Cocoa/chocolate	2/5	2/5	Decrease in AS (chronically) and in WR (chronically, acutely)	Ideal dose not known Effect of milk chocolate? Although effects are flavonoid-related, exact mechanisms to be elucidated
Alcohol	2/5	4/5	Decrease in AS and WR	Most cross-sectional studies do not discriminate between drinks Need investigation: alcohol or flavonoids responsible? Differential effect of red wine not established Mechanisms to be elucidated
Salt	2/5	3/5	Positive association with AS in cross-sectional studies Beneficial effect of sodium restriction (intervention studies)	Mechanisms to be elucidated
Smoking	4/5	4/5	All types (acute, passive, cigarette, cigar) induce increase of AS and WR	More smoking cessation studies needed to assess the reversibility of detrimental effects
Obesity/Weight loss	2/5	3/5	In most studies obesity is associated with increased AS, but in some with decreased Central obesity most likely detrimental Weight loss improves AS (independently of the type of diet)	Discrepant results of studies to be reconciled Mechanisms to be elucidated Pressure-dependent or -independent effect?
Exercise	3/5	3/5	Beneficial effect of aerobic exercise, unfavourable of resistance, neutral of combined	Conclusions blurred by the natural tendency of persons with already elastic arteries to be more easily engaged in exercise Level (frequency/intensity) of exercise that is beneficial to be defined
Mental stress	2/5	2/5	Not all studies agree, probably increase in AS and WR	Discrepant results in studies to be reconciled Chronic effect to be investigated Mechanisms to be elucidated

^a Rating of pathophysiological background and clinical evidence was made according to the authors' personal evaluation on an arbitrary scale. AS: aortic stiffness; WR: wave reflections.

properties. Importantly enough, several lifestyle elements interplay, having effects that are even synergistic.

The present review will present data regarding aspects of nutrition, obesity/weight loss and physical activity, smoking and mental stress (Table 1). Available studies are of the following categories, each having particular strengths but also limitations: Pathophysiological studies elucidate mechanisms and solidify the theoretical background, but they do not necessarily extend to clinical associations and benefit. Cross-sectional or population studies reveal associations, usually independent, but they do not establish causal relationships. Prognostic studies dealing with events in a long-term follow-up are the most important, but unfortunately those are the studies that we practically lack at present. Studies of a special nature that fall into all of the above categories are intervention studies (i.e. assessing the effect of the addition or removal of a parameter on arterial function). These studies are very insightful providing evidence of etiological associations.

As keys of reading this review one should keep in mind that arteries of different nature (elastic, muscular or mixed) do not necessarily behave in the same way and results of studies in one vascular bed should not be extrapolated without caution to another. Furthermore, the terms stiffness and wave reflections, despite the latter integrating the first and usually (but not always) [1] changing towards the same direction, are not interchangeable but they are complimentary and of specific importance each. Finally, since this review is oriented towards arterial stiffness and wave reflections, reference to endothelial function will made when this is necessary to explain mechanistic links, given the regulatory role of endothelium on arterial stiffness.

2. Diet/nutrition

The effect of various dietary/nutritional components on arterial function has been studied extensively. Research has focused especially on caffeine and coffee, tea, cocoa, wine and other flavonoid-containing foods and beverages, antioxidant vitamins, and sodium.

2.1. Coffee-caffeine

Surprisingly enough, the effect of coffee consumption on cardiovascular risk has not been defined yet. Results of studies vary from a positive to a neutral or to even a J- or a U-shape association of coffee consumption with cardiovascular risk. Genetic predisposition for rapid caffeine metabolism may account for these discrepancies.

The main vasoactive substance in coffee is caffeine which, as we [2-4] and others [5,6] have shown, exerts an acute detrimental effect on aortic stiffness and wave reflections, both in normal subjects and in hypertensives. The ingestion of caffeine results in a sustained impairment of arterial stiffness, which lasts for at least three hours. Interestingly, the unfavourable effect of caffeine is more evident in central hemodynamics than in peripheral (brachial) pressure [2]. Furthermore in cross-sectional studies we have shown a positive association of chronic coffee consumption with increased aortic stiffness and wave reflections in healthy subjects [7] and with increased wave re-

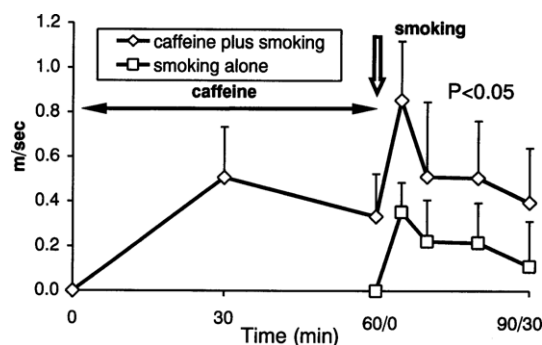


Figure 1. Pulse wave velocity response during the combined caffeine and smoking study. Each line represents *response* defined as net caffeine and smoking effect minus placebo and sham smoking effect (diamonds) or net smoking effect minus sham smoking effect (rectangles) at each time point. When smoking followed caffeine intake, pulse wave velocity reached a total increase of 0.85 m/s, 0.17 m/s in excess of the mere sum of caffeine effect (0.33 m/s) alone and smoking effect alone (0.35 m/s). *P* values on the graphs refer to the *interaction* between caffeine and smoking. Error bars: SEM. Reprinted with permission from Vlachopoulos et al. (2004) [4].

flections only in hypertensives (C. Vlachopoulos et al., unpublished data). The latter denotes that the stiffening effect of coffee in the aorta is probably less prominent in the already stiff aortas of hypertensives than in normal aortas. In other words, it appears that coffee does not have a stiffening effect on the aorta additive to that of hypertension.

Caffeine exerts its main cardiovascular effects through the antagonism of adenosine and the release of catecholamines, both resulting in vasoconstriction. Beyond this, chronic coffee consumption is associated with increased inflammatory markers, another possible way by which coffee may induce vascular dysfunction [1].

An important issue is whether substances other than caffeine contribute to the effect. In preliminary studies we have shown that coffee increases arterial stiffness more than its contained caffeine and that de-caffeinated coffee also increases arterial stiffness to a certain extent (C. Vlachopoulos et al., unpublished data). In line are studies that show that de-caffeinated coffee has cardiovascular effects. More specifically, it has been shown that it augments blood pressure and muscle sympathetic nervous activity, denoting that substances other than caffeine are responsible for cardiovascular activation [8].

Coffee consumption is very frequently combined with smoking. Interestingly enough, the combination of these two habits has a synergistic detrimental effect on aortic stiffness and wave reflections, both on an acute and on a chronic basis (Figure 1) [4].

2.2. Tea

Tea consumption has been associated with decreased cardiovascular risk, although there is no consistency in the findings of all studies. Tea consumption has an acute and short-term (i.e. one month) beneficial effect on endothelial function, mainly attributed to its flavonoid content. To date, only acute studies on arterial stiffness and wave reflections are available. Contrary to studies on endothelial

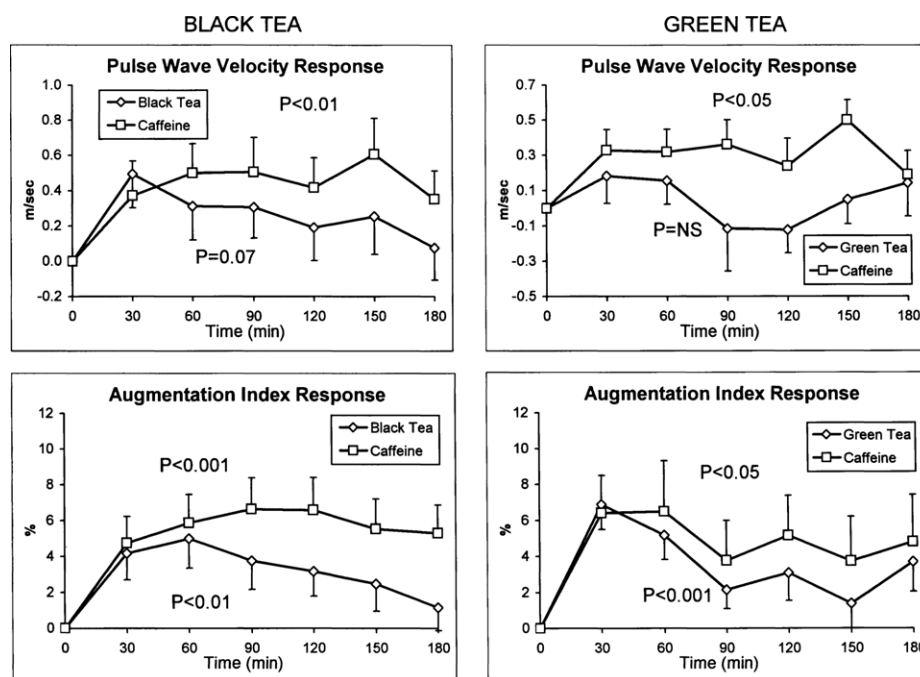


Fig. 2. Pulse wave velocity and augmentation index response during the *black tea* and the *green tea* study. Each line represents response defined as net tea or caffeine effect minus hot water effect at each time point. *P* values refer to the response of tea or caffeine compared to hot water during the whole study duration. Error bars: SEM. Reprinted with permission from Vlachopoulos et al. (2006) [9].

function, tea has an acute unfavourable effect on aortic stiffness and wave reflections. As we have shown, both black and green tea increase acutely wave reflections in normal subjects [9]. This effect becomes evident promptly after tea consumption (30 minutes), which is actually the time that it takes for caffeine to absorb. On the other hand, the effect of tea on aortic stiffness is less straightforward. Green tea has no significant effect, whereas black tea increases aortic stiffness for less than 2 hours. For comparison, the same amount of caffeine contained in black tea, when ingested alone, has a pronounced effect on aortic stiffness and wave reflections that lasts for 3 hours (Figure 2). A unifying explanation is that caffeine contained in tea increases arterial stiffness. Flavonoids, which notably take more time than caffeine to absorb (90-120 min) have a counterbalancing beneficial effect resulting in a total neutral effect in arterial stiffness with green tea (high concentration in flavonoids) and a delayed neutral effect with black tea (lower concentration in flavonoids).

2.3. Cocoa-Chocolate

Originally cultivated in Mesoamerica, and considered a medicine and a "food of the Gods" by the Aztecs, cocoa acquires a scientific basis for its beneficial effects in our era. Habitual chocolate consumption is inversely associated with blood pressure and, importantly, cardiovascular risk. Its blood-lowering effect was originally noted in Kuna Indians who live in isolation, drink large amounts of cocoa, and have very low prevalence of hypertension. When they migrate to an urban area their blood pressure rises, denoting a protective effect of environmental/nutritional factors (most likely cocoa) in

their island of origin. We have recently shown in a cross-sectional study that chocolate consumption is inversely associated with aortic pulse wave velocity and wave reflections in healthy subjects. Consumption of at least 12 grams of chocolate per day was associated with a significant decrease in carotid-femoral pulse wave velocity and in augmentation index. Furthermore, increasing intake of chocolate is associated with a decrease of central (aortic) systolic pressure and of central pulse pressure, but not of peripheral (brachial) pressure, denoting that its beneficial effect is not always evident when only peripheral pressures are measured (C. Vlachopoulos et al., unpublished data).

Most intervention studies have used *cocoa* and *dark chocolate* rich in cocoa flavonoids, because their beneficial effect is mainly attributed to their high flavonoid content. Both of them exert a beneficial acute and short-term effect on endothelial function, as it has been shown both in healthy subjects and in subjects with cardiovascular risk factors, or cardiovascular disease. Dark chocolate results acutely in a decrease in wave reflections in normal individuals [10]. Aortic stiffness is not largely affected by acute chocolate consumption, while a tendency to decrease at a later stage (3 hours or more) begins to show [10]. These taken together imply that cocoa exerts a vasodilatory effect on small and medium-size arteries possibly due to increased flavonoid-related NO bioavailability and/or increased prostacyclin production. The effect of the more largely consumed *milk* chocolate is not known. Effects are anticipated to be similar, although not necessarily identical, because milk chocolate contains much less flavonoids than dark chocolate, and also because flavonoids are absorbed to a lesser degree when milk is present.

2.4. Alcohol and alcoholic drinks

Moderate alcohol consumption is associated with decreased cardiovascular risk. Similarly to studies regarding cardiovascular risk, most cross-sectional studies on the effect of alcohol on arterial function do not discriminate between alcoholic drinks. In keeping again with these general studies, a J- or U-shaped curve has been demonstrated between alcohol consumption and aortic stiffness and wave reflections both in men and in women [11-14]. Possible mechanisms involved include increase in high density lipoprotein cholesterol, while, interestingly enough, the inflammatory effect of alcohol shows a U-shaped behaviour. The effect of alcohol on endothelial function is not so clear. Experimental data suggest that moderate alcohol consumption increases NO production, while heavy alcohol drinkers have impaired endothelial function. We have shown that the acute effect of pure alcohol is neutral; the vasodilation induced both in resting and hyperemic diameter of the brachial artery results in a non-significant change in flow-mediated dilatation [15].

Red Wine: Studies, particularly acute intervention ones, have focused specifically on red wine given the possible preponderance of this alcoholic drink in reducing cardiovascular risk (French paradox). Red wine decreases aortic stiffness and wave reflections acutely. Studies with de-alcoholized wine have shown that part of the effect is due to alcohol-induced vasodilation [14,16] and part to the high flavonoid content [17]. The short-term (6 weeks) effect of red wine has been recently studied in postmenopausal women. Neither red wine, nor de-alcoholized red wine induced any changes in wave reflections and central hemodynamics [18].

As regards endothelial function, the high flavonoid content of red wine, high in antioxidant capacity, has been pointed as the substance responsible for the beneficial effect of this drink on endothelial function.

2.5. Other foods and vitamins

Isoflavones - another type of flavonoids, found in soy and in red clover - have been shown to reduce systemic arterial compliance and aortic pulse wave velocity when given for a period of 5-10 weeks [19]. The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, found in fish, have a beneficial effect on arterial stiffness [20].

Furthermore, vitamin C (ascorbic acid) and vitamin E seem to favourably affect arterial elastic properties [21].

2.6. Salt

High salt intake has been associated with increased aortic stiffness in the general population [22] and in normotensive adults. Furthermore, salt-sensitive hypertensives have increased arterial stiffness compared to salt-resistant subjects with the same blood pressure levels [23].

High-salt diet results in a decrease in femoral distensibility in diabetic subjects compared to non-diabetics, which is reversed with angiotensin converting enzyme inhibition [24]. More importantly, a relatively brief period of sodium restriction decreases arterial stiffness. The

same effect has been observed promptly, just one week after sodium restriction, in older adults with systolic hypertension [25].

The detrimental effect of high sodium consumption on arterial stiffness may be attributed, at least partly, to endothelial impairment. Furthermore, and probably as a consequence of the endothelial dysfunction, structural changes in the arterial wall further deteriorate elastic properties.

3. Smoking

Smoking is the most important modifiable risk factor for coronary artery disease. The effect of passive and active smoking on arterial elastic properties has been extensively studied. Active and passive smoking result *acutely* in stiffening of elastic and muscular type arteries and in enhancement of wave reflections [4,26,27]. Cigar smoking is not innocent either; it stiffens aorta and enhances wave reflections in healthy young smokers [28].

Many studies have demonstrated the detrimental *chronic* effect of active and passive smoking on arterial elastic properties. The chronic detrimental effect of smoking on the stiffness of both elastic and muscular type arteries and on wave reflections has been documented [4,27,29-31]. No relation is observed between duration and/or intensity of smoking and arterial dysfunction. It seems that even small quantities of smoking are able to produce its deleterious effects.

A significant part of the unfavourable effect of smoking on aortic stiffness is pressure-independent as we have shown using high-fidelity invasive methods describing the behaviour of the pressure-diameter loop [26]. Endothelial dysfunction plays a key role; smoking leads to the release of free-radical species and induces both functional and morphological changes in the endothelium, ultimately leading to decreased NO bioavailability [31].

As mentioned above, smoking and caffeine have a synergistic effect on arterial function when combined [4]. Importantly, the detrimental effect of smoking is potentially reversible after smoking cessation [31].

4. Obesity-weight loss and exercise

4.1. Obesity-weight loss

Obesity is not strictly a lifestyle component, but it is rather a disease. However, it is discussed in this review because it is largely the consequence of unhealthy diet and lack of exercise.

Obesity and especially central (abdominal) obesity is associated with increased cardiovascular risk. The effect of obesity on arterial stiffness has been extensively studied. Most studies have shown that obesity is associated with increased arterial stiffness in various arterial beds [32-34], although there are a few studies with opposite results [35]. Multiple explanations for this discrepancy have been proposed. It seems that different vascular beds are affected in different ways by obesity. Furthermore, the decreased stiffness found in some studies is related to an increase in arterial diameter and to a hyperdynamic circulation with decreased systemic vascular resistance.

Finally, alterations in perivascular structures possibly offer less resistance to vessel distension [33].

Interestingly, the negative impact of obesity on arterial stiffness has also been investigated in children and adolescents [36,37]. Obese children have increased arterial stiffness and increased carotid intima-media thickness, denoting a faster progression to atherosclerosis [37].

Central fat accumulation has gained specific attention. In a cross-sectional study with prospective analysis it was found that truncus subcutaneous fat accumulation during adolescence was associated with increased central arterial stiffness at the end of the follow-up (age 36) [33]. On the other hand, peripheral fat, i.e. in the limbs, is associated with decreased arterial stiffness, possibly involving mechanisms such as those mentioned above. The main pathophysiological mechanisms linking central obesity and vascular dysfunction include the production of adipocytokines, with detrimental metabolic effects and an inflammatory stimulation. Also, high leptin level is independently associated with decreased radial artery distensibility in obese subjects [38].

The effect of obesity on arterial function is further stressed when changes in weight occur. As demonstrated recently, changes in body weight in a 2-year follow-up were positively associated with changes in aortic pulse wave velocity. While weight gain increased large-artery stiffness, weight loss had the opposite effect [39]. The beneficial effect of weight loss has been demonstrated also in various populations [32,40-42] and is independent of the diet used (meat- or plant-based) [41]. The improvement in arterial elastic properties observed with weight loss is largely explained by the concomitant reduction in blood pressure [41]; however the reduction in aortic pulse wave velocity observed with weight loss was independent of blood-pressure changes in one study [39].

4.2. Exercise

Exact definition of the association between exercise and arterial stiffness is often cumbersome because it may differ depending on the type (aerobic, resistance, combined) and the amount of exercise (leisure, athletic). Furthermore, it should be kept in mind that the initiation point of the series of events is difficult to define. In other words, while exercise may in itself lead to an improvement in elastic properties, it may also well be that those with already elastic arteries can more easily exercise for this very reason; thus, they are more often engaged in such activities, setting a positive feedback mechanism in operation.

Aerobic (endurance) exercise has a beneficial effect on arterial function. Increased aerobic capacity has been associated with reduced aortic stiffness and wave reflections [43]. Age-related increases in central arterial stiffness are blunted in postmenopausal women who are physically active [44]. The effect of regular exercise is evident mainly in central arterial stiffness [44], while peripheral arterial stiffness may not be altered [44]. An interesting finding was that the level of fitness is associated with large-artery stiffness even in children aged 9-11 years, denoting a possible protective effect of aerobic exercise

even from this age [45]. The beneficial effect of physical activity has also been demonstrated in a study of female twins, in which subjects at high genetic risk of high augmentation index with leisure-time physical activity had lower augmentation index than non-participants [46].

The beneficial effect of aerobic exercise on arterial elastic properties has been elucidated using intervention studies. Aerobic exercise increases acutely total arterial compliance [47]. And this is probably related to vasodilation. Regular aerobic exercise has the potential to ameliorate central arterial stiffness in middle-aged sedentary men [48]. However, the same effect was not observed when patients with isolated systolic hypertension were trained for 8 weeks [49].

The mechanisms through which habitual exercise exerts its favourable effects on arterial elastic properties are not fully understood. Structural changes may ensue. In an interesting study in athletes performing asymmetric training of the two arms (hammer throwers and baseball players) there was a difference in radial artery structure between the two arms, which was accompanied by a significant increase in distensibility of the artery (muscular type) of the dominant arm [50]. The role of endothelium is unequivocal and a possible anti-inflammatory effect may also play a part.

Resistance (strength) exercise does not have the same effect on arterial stiffness as aerobic exercise. In fact, resistance exercise actually increases arterial stiffness acutely [51] and resistance-trained athletes have increased arterial stiffness [52]. Furthermore, the detrimental effect of resistance exercise on arterial stiffness was shown in an intervention study, in which four months of resistance training resulted in a significant increase in arterial stiffness; this increase was completely reversed after four months of detraining [53].

Finally, athletes performing *combined* aerobic and strength training, such as rowing, exhibit decreased aortic stiffness, denoting that endurance training is able to negate the stiffening effects of strength training [54].

5. Mental stress - emotional status

Mental stress is linked to increased cardiovascular morbidity and mortality. Acute mental stress may lead to myocardial ischemia, infarction, left ventricular dysfunction with normal coronary arteries, or even sudden cardiac death. Myocardial ischemia caused by mental stress occurs at a lower double product (heart rate \times blood pressure) than exercise. Impairment of endothelial function has been proposed to explain this, but increases in arterial stiffness and wave reflection may also account for it.

The effect of *acute* mental stress on arterial function has been examined in various vascular beds using different methods of inducing mental stress. Compliance of the muscular radial artery was found to be decreased by mental stress in healthy subjects [55], but it was not affected in normotensive offspring of hypertensives [56]. In another study, although mental stress resulted in a reduction in arterial compliance both in normotensive and mildly hypertensive individuals, wave reflections were not

increased in either of these two groups [57]. Interestingly enough, brief periods of mental stress can have an enduring effect on arterial stiffness, leaving inferences for the effects of more prolonged or intense stimuli in everyday life. Indeed, we have recently demonstrated that a 3-min arithmetic mental stress results in an at least 60-minute increase in aortic stiffness and wave reflections in healthy subjects [58]. Taken from the exactly opposite angle, good mood appears to have a beneficial effect on arterial stiffness. Preliminary data from our laboratory suggest that laughter reduces aortic pulse wave velocity.

Data on the effect of *sub-acute or chronic* mental stress on arterial function are lacking. Most studies have focused on psychiatric disorders, such as depression, which are associated with endothelial dysfunction even in remission periods; however central hemodynamics do not seem to be altered in major depression.

6. Perspectives

The awareness of both the medical community and the public on the effect of lifestyle on cardiovascular disease is rapidly increasing. An impressively growing body of evidence attests to an independent effect of lifestyle on arterial function. It is likely that some of the expected cardiovascular benefits of an integrated "lifestyle approach", like the one recently proposed by the American Heart Association, are mediated, at least in part, by an improvement of arterial elastic properties and/or endothelial function. Perhaps it is not long before terms like "behavioural arteriology" are coined into our clinical practice.

Disclosure of interest

There is no potential conflict of interest.

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