Narrative review

Task force on: 'Early markers of atherosclerosis: influence of age and sex'

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Atherosclerosis and its complications are the most important causes of death all over the world, especially in Western countries. Diet habits, modern stress life, smoking, sedentary way of life and an involvement of genetic pattern of individuals lead to a sure degeneration of quality of life increasing the risk of atherosclerosis development. For this reason, the main purpose of actual medicine is to identify all the markers that could allow the physicians to evaluate the first moments of the development of this dangerous pathological process. The aim is to reduce the speed of its evolution, trying to delay indefinitely the risk coming from the morphological alterations of the vessels. 'Endothelium function' could allow physicians to detect the first moment of the natural history of atherosclerosis process. Its impairment is the first step in the degeneration of vascular structures. Many methods [flow-mediated vasodilatation (FMD); antero-posterior abdominal aorta diameter (APAO); intima-media thickness of the common carotid artery (CCA-IMT); arterial stiffness; and so on] try to evaluate its function, but many limitations come from general population characteristics. A standardization of the methods should take into account individuals' peculiarities. Two elements, not modifiable, should be taken into account for vascular evaluation: age and sex. The aim of this review is to outline the linkage among age, sex and instrumental evaluation of patients considered for a noninvasive assessment of their cardiovascular risk profile.

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Introduction

Atherosclerosis and its complications are the leading causes of death worldwide. Its pathogenesis deals with inflammation and autoimmune aspects well developed in the literature.[1] It seems to grow from childhood. In fact, lipid entrapment, oxidation and their shape-changing in vessel walls lead to a chronic inflammatory state, which turns transformation of the former 'fatty streaks' into a real fibrous plaque, susceptible to future rupture, thrombosis and stenosis.

In 1976, Ross and Glomset[2] outlined the inflammatory nature of the atherosclerotic process and its relationship with all the components of endothelial organ and its cells (circulating or adhering to the vessel walls). International research[3–5] tried to explain the fundamental mechanism at the basis of the atherosclerosis, outlining the great influence of damaged vascular endothelium and circulating factors in inducing the development of plaque.

Moreover, hypertension,[5] obesity,[6] smoking,[7] dyslipidemia,[5] diabetes[5] and even age[8] and sex[9] have an important role in continuing such a systemic illness, leading to a faster growth during individuals' life period.

Research developed early markers of atherosclerosis. Instrumental examinations [intima–media thickness of common carotid artery (CCA-IMT), arterial stiffness, ankle-brachial index (ABI), antero-posterior abdominal aorta diameter (APAO), flow-mediated vasodilatation (FMD), left ventricular hypertrophy (LVH) and so on] have been employed to evaluate its function. The aim of this review is to evaluate the effect of age and sex on the early markers of atherosclerosis, in order to better understand how such parameters can influence the precocious identification of the disease.

Brachial artery flow-mediated vasodilatation

The endothelium is an autocrine–paracrine organ that plays an important role in regulating vascular tone by

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modulating blood flow in response to the action of substances that act on endothelial cells.

Its impairment, so-called 'endothelial dysfunction', is the earliest event in the atherosclerotic process.[10]

The FMD technique is a validated instrumental tool able to detect endothelial function status.[10]

Implementing rules

An electronic probe is positioned 4–5 cm above the elbow to obtain right brachial artery longitudinal scanning. After 1 min resting period in supine position, a blood pressure (BP) cuff is inflated to 250 mmHg for exactly 5 min,[11] then rapidly deflated. The following reactive hyperemia induces an increase in brachial artery diameter due to nitric oxide production. The FMD is the ratio of diameter change (maximum − baseline) to baseline:

$$\text{FMD} = [(\text{post-hyperemia diameter} - \text{baseline diameter})/\text{baseline diameter}] \times 100.$$

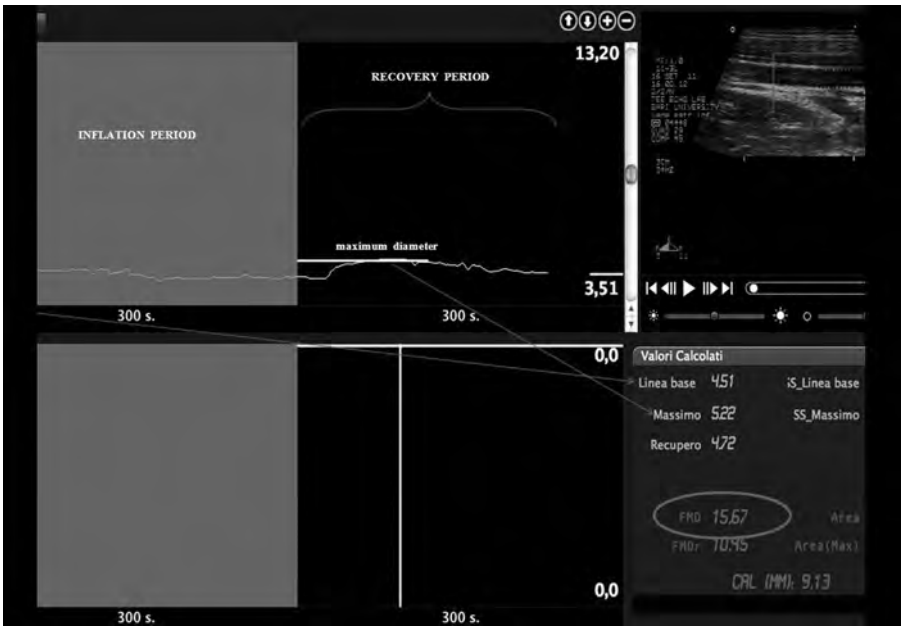
(see also Fig. 1). Normal values are those greater than 5–10%.[11]

Clinical impact

Sex seems to really influence artery dilatation induced by nitric oxide. Celermajer *et al.*[12] first demonstrated that a reduced FMD is related to older age ($r = -0.34$, $P < 0.0001$) and sex. In men, FMD was preserved in individuals aged 40 years or less but declined thereafter at 0.21% per year. In women, FMD was stable until the early 50s, after which it declined at 0.49% per year ($P = 0.002$ compared with men). Thus, age induced progressive endothelial dysfunction in normal humans, and this occurred earlier in men than in women. In women, a steep decline starts at menopause. Tomiyama *et al.*[13] also found a negative correlation among FMD and age/sex (beta = −0.19, $P < 0.01$, beta = −0.024, $P < 0.01$, respectively) and this provided evidence as to how these could be considered independent variables related to the impairment of FMD. Jensen-Urstad and Johansson[14] highlighted the relationship between sex and age on vascular function. FMD-induced vasodilatation is smaller in women at 55 years of age than at 35 years of age, and similar in 35- to 55-year-old men and in men and women at 55 years of age.[14] The Cardiovascular Risk in Young Finns Study[15] exalted FMD reproducibility differences between sexes and postulated that this could be due to differences in risk factors and vessel size.

Interestingly, a persistently reduced FMD after short-term antihypertensive treatment was predictive of cardiovascular events in a cohort of postmenopausal women.[16] However, Hu *et al.*[17] showed a similar predictive value of FMD in men and women without significant coronary artery disease (CAD), as also shown in hypertensive patients.[18] No explanation had been proposed for this,

Fig. 1



A sample case of brachial artery flow-mediated vasodilatation evaluation. It is the percentage increase in brachial artery diameter between baseline and after-deflation measurements.

but the difference could be due to natural differences between sexes. Estrogen imbalance between sexes could partially explain the discrepancy.[19]

In conclusion, it is well known that age alters the vascular structure naturally and independently. Such degeneration impairs endothelial function and, consequentially, FMD, even considering 'healthy' individuals, that is persons with no cardiovascular risks.[20] Age 'per se' is a natural predictor of impaired endothelial function and for this reason should be well analysed when physicians would like to detect the early moments of the atherosclerotic process. Ryliskyte *et al.*[21] tried to extrapolate the normative value of FMD in patients with low cardiovascular risk profile. They analysed normal individuals according to their different ages (115 individuals with mean ages $44.19 + 12.23$ years and a range of 26–83 years), in order to point out the normative value of FMD at different ages of life. Ciccone *et al.*,[22] by considering only children, measured the normal value of FMD of brachial artery in young age as almost equal to 10% (men: $8.29 + 3.21\%$ and women: $8.29 + 3.48\%$) independent of sex. With increasing age, FMD reduces its value (to 6%), varying according to sexual characteristics.

Further larger, possibly multicentre, studies are important to assess the real burden that age and sex could have on FMD and the role of many biases that affect FMD evaluation[23–26].

Antero-posterior abdominal aorta diameter

Implementing rules

APAO is defined as the maximal external cross-sectional measurement, calculated as the distance between the near and the far walls of the abdominal aorta. Measurements were performed at 0.5, 1 and 2 cm above the umbilicus and were expressed in centimetres[27] (Fig. 2).

Clinical impact

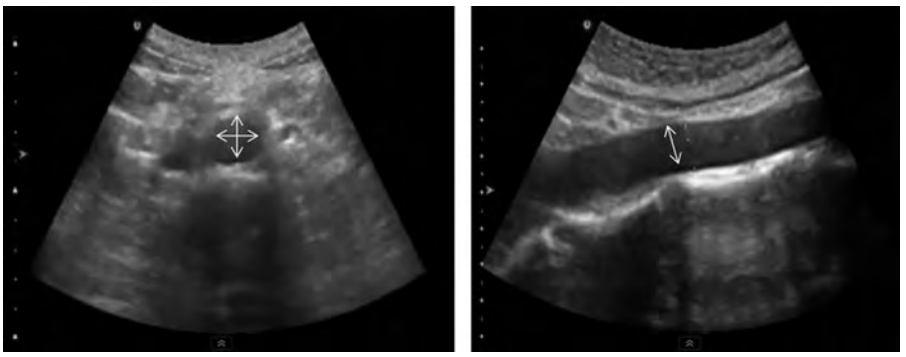
The APAO has been always related to abdominal aortic aneurysms, but it is recently becoming an atherosclerotic marker,[28] influenced by sex and age. Norman *et al.*[29] indicated infrarenal aortic diameter as a real predictor of all-cause mortality by analysing 12 203 men aged 65–83 years. Patel *et al.*[30] reached the same results in a female population.

APAO as an atherosclerotic cardiovascular risk factor is a well-developed issue in the literature.[31] Sonesson *et al.*[32] showed no differences in aortic diameter between men and women with smoking habits, although women were characterized by an aortic stiffness higher than men, and this sign seemed to indicate that the aorta of women might be more vulnerable to smoking with regard to stiffening and degeneration than the aorta of men. Men with an increased APAO had a higher incidence of peripheral vascular diseases than the opposite sex.[33,34] Male sex seems to be an important determinant in developing enlargement of abdominal aorta diameter and, consequentially, cardiovascular ischemic diseases (i.e. acute coronary syndromes and proven coronary stenosis).[28,35]

An important proceeding about the matter comes from the manuscript of Ciccone *et al.*[27] They considered young women suffering with polycystic ovary syndrome (PCOS) and showed that increased APAO is the earliest arterial alteration in women with PCOS, preceding CCA-IMT alterations. The work links age and sex in the evaluation of APAO: female sex and age influence the development of increasing abdominal aorta diameter and, in this way, worsen the natural history of the atherosclerotic process.

Grimshaw and Thompson,[36] although considering only men in their evaluation, found that an increase in aortic diameter could impair prognosis in patients. Similar results came from the research by Palombo *et al.*,[37] once again concerning measuring of abdominal aorta diameter in old age but in patients with abdominal aorta aneurysm. Wilmink *et al.*,[38] instead, investigated the natural relationship between age and APAO. Data from their analysis of 3066 women and 8270 men added evidence that APAO effectively increased with age.[38] Older

Fig. 2



Measurements of antero-posterior abdominal aorta diameter.

patients seemed to be at a high risk of developing a worsening in aortic diameter than younger ones.[38] Long *et al.*[35] and Allison *et al.*[28] confirmed these data. The relationship between APAO and age had been well shown in a 'visual and anato-pathological' analysis by Sawabe *et al.*[39] in 833 consecutive autopsy cases (616 men and 217 women). The age at death ranged from 20 to 94 years, with an average of 59.2 years. They noticed that age really contributes to aortic dilatation, more than atherosclerotic burden. Thus, age influences the analysis of APAO.

Intima-media thickness of the common carotid artery

CCA-IMT is the most international validated cardiovascular risk marker.[40] Many works[41–44] have revealed its importance in the early detection of atherosclerosis.[45]

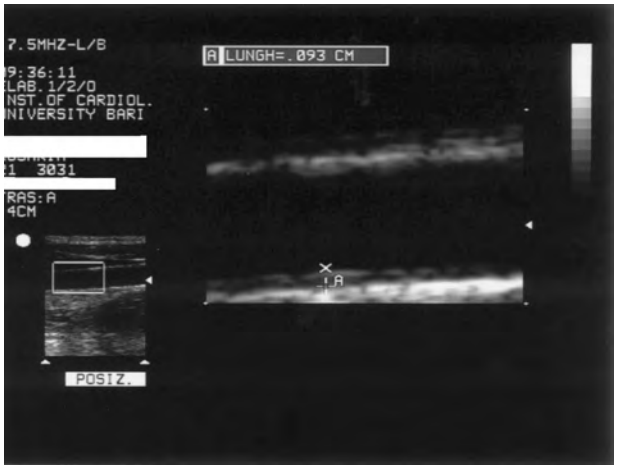
Implementing rules

Patients are placed in a supine position, the neck extended and turned contralaterally by about 45°. The CCA-IMT is defined as the distance between the lumen-intima and media-adventitia borders of the vessel, ultrasonographically identified by a double hypoechoic line not projecting into the vessel lumen[46] (Fig. 3). Echo-measurements should be made in three zones: proximal zone: about 2 cm above the flow-divider; distal zone: about half centimetre above the flow-divider; and middle zone. The arithmetical mean CCA-IMT value (mCCA-IMT) should be calculated.

Clinical impact

Age and sex could impair CCA-IMT. The CAMP study by Ciccone *et al.*[42] involved four Italian centres (Lecco; Pisa; Bari; Palermo) in order to establish the normal mean Italian values of CCA-IMT, adjusted for age and sex. One thousand and seventeen healthy individuals without any cardiovascular risk factors (596 men and 421 women), aged between 22 and 85 years (mean 58.5 + 13.2 years), were studied. The data allowed tables of percentiles for normal CCA-IMT values in Italy to be drawn up according to sex and age. CCA-IMT was positively correlated with age and mean values were higher in men than in women. Also, Novo *et al.*[47] pointed out the importance of CCA-IMT and carotid plaque in picturing the cardiovascular risk profile of patients older than 45 years, underlining the role of CCA-IMT in evaluating the preclinical stages of the atherosclerosis.[48]

Fig. 3



Carotid intima-media thickness evaluation.

Sex is 'per se' a known parameter able to heavily influence the evaluation of CCA-IMT. Such consideration comes not only from the previous work of Ciccone *et al.*[42] but also from other work.[15] The research by Böhm *et al.*[49] on 267 healthy pupils (aged 6–17 years) pointed out a clear difference between sexes for CCA-IMT values since childhood. These findings contrast those of the MESA study[50] wherein no influence of sex on CCA-IMT was found.

Studies[51,52] underlined a negative influence of female sex on CCA-IMT. The importance of female sex emerges by considering the effects of hormone changes during women's life.[53] Ciccone *et al.*[54] demonstrated that obese women affected early on by Hashimoto's thyroiditis develop impairment of vascular structure at carotid level. The same results are reported in premenopausal or menopausal women.[43,55] On the contrary, men had an increased cardiovascular risk profile just in relationship to their own habits and constitution.[56]

The CAMP study[42] showed age influencing CCA-IMT, due to the natural history and progression of atherosclerotic process. Barra *et al.*[57] underlined the early increase of CCA-IMT in children whose relatives/parents suffered with premature myocardial infarction. The Cardiovascular Risk in Young Finns study[58] indicates that children with risk factors have increased atherosclerosis progression rate in adulthood, although, according to Ygando *et al.*,[59] cardiorespiratory fitness improves CCA-IMT values even in adults, that is in patients in whom vessel structural alterations had become more severe. Finally, Takato *et al.*[60] suggested that sexual differences exist in the relationship with CCA-IMT and age increase. Thus, the CAMP study[42] is a really basic study, as it points out the natural development of CCA-IMT values through years in an Italian population and it greatly links the age of patients to their own sex and to CCA-IMT values. These considerations really improve the diagnostic power of CCA-IMT and help physicians to better picture the clinical conditions of the patients.

Nevertheless, despite the influences of age and sex on CCA-IMT, literature data[61] affirm the importance of CCA-IMT as a surrogate parameter of systemic

atherosclerotic process in the assessment of cardiovascular risk profile of individuals since the early periods of their lives.

Ankle-brachial index

Implementing rules

The ABI is a simple, noninvasive test, measuring the SBP from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries after the patient has been at rest in the supine position for 10 min.[62] It is obtained by dividing the highest ankle systolic pressure by the highest brachial systolic pressure.[62]

Clinical impact

The ABI is used both to screen for peripheral arterial disease (PAD) and to establish its diagnosis with a high degree of accuracy (sensitivity: 79–95%; specificity: 95–100%). A normal ABI is above 1.10, whereas PAD is generally defined as a resting ABI of 0.90 or less.[62] Considered before as a basic tool to quantify the severity of occlusive disease, the ABI has more recently become a marker of cardiovascular risk, associated with an increased risk of myocardial infarction and death and able to improve Framingham risk score prognostic role.[63]

Age and sex could impair ABI. A low ABI is common in the elderly, with a prevalence more than 25% in individuals older than 85 years,[64] associated with increased risk of death, global cardiovascular diseases (CVDs), coronary heart disease and symptomatic PAD.[65] A low ABI in the elderly has been shown to increase risk (more than six-fold) for coronary heart disease mortality in both men and women (mean age: 66 years) with large-vessel PAD, as Criqui *et al.*[66] demonstrated. Interestingly, Murabito *et al.*[67] found that a low ABI was both independently and inversely related to the risk of stroke or transient ischemic attack in elderly persons with and without CVD at baseline, but not with risk of CAD or death. Nevertheless, methodological pitfalls could be outlined: diabetic patients or very elderly individuals' pressure cannot be abolished by inflation of an air-filled BP cuff (non-compressible pedal arteries); a high ABI is thought to represent stiff arterial walls, potentially including medial arterial calcification. Therefore, the value for the ankle artery sometimes is not an accurate measure of intra-arterial pressure but rather a falsely high value due to stiffness in the arterial wall. However, the relative risk of cardiovascular mortality in the low ABI cohort was increased approximately three-fold to four-fold in a cohort of 1537 elderly men and women followed in the Systolic Hypertension in the Elderly Program.[68]

Among older individuals, the prevalence of PAD is similar to, or even slightly higher, in women than in men. McDermott *et al.*[69] found that at 47 months of follow-up, women with PAD were more likely to become unable to walk for 6 min continuously, and they had a higher incidence of mobility loss and faster declines in 6-min walk distance than in men with PAD, maybe due to baseline sexual differences (lower calf muscle area and reduced knee extension strength in women) in functional performance. Among Spanish people, the effect of calculating ABI on the reclassification of cardiovascular risk categorized by the principle functions (Framingham-Wilson, REGICOR and SCORE) induced changes in category risk. Reclassification was stronger in women; according to SCORE, the high-risk category increases by 50%; according to Framingham-Wilson, it increases by 78.6%; and according to REGICOR, it increases by 151.6%.[70] Moreover, patients with ABI less than 0.9 were older, more frequently men, and had a worse profile for all the cardiovascular risk factors.[70]

The importance of sex emerges above all when considering the effects of hormone changes throughout women's life. Several population-based studies have suggested that the prevalence of a low ABI is more common in women.[71] In patients undergoing elective coronary angiography, women had a higher prevalence of PAD than in men and a lower prevalence and severity of CAD, although the mechanisms are still unclear.[71] Intriguingly, men are more than twice as likely to be selected for lower extremity revascularizations, even after adjusting for limb salvage, age, ABI, comorbidity and smoking.[72]

Genetic polymorphism could influence ABI index.[73] The GG genotype of single nucleotide polymorphism rs11066001 of BRAP (a protein participating in the lymphotoxin-alpha-associated inflammatory pathways, associated, if altered, with myocardial infarction) in women was significantly associated with a lower ABI value than in men with the same genotype, maybe the cause is a different sexual action of release of inflammatory molecules associated with this gene.

Left ventricular hypertrophy

LVH is a compensatory process that represents an adaptation to increased ventricular wall stress in hypertension. It is also the first step towards the development of overt clinical disease such as congestive heart failure, ischemic heart disease and sudden death. An increasing prevalence of vascular alterations in patients with increased left ventricular mass and/or concentric geometry has been demonstrated.[74,75] Conversely, atherosclerosis can adversely affect left ventricular dimensions, volumes, wall thickness and mass.[76,77] Echocardiography is much more sensitive than electrocardiography in LVH detection.[78]

Implementing rules

To estimate LVH, we measure interventricular septal and posterior wall thickness and left ventricular internal dimension. Parasternal long-axis acoustic window could be used.[78] Systolic and diastolic left ventricular internal dimensions should be measured at the level of the left ventricular minor axis, approximately at the mitral valve

leaflet tips by 2D images or 2D-targeted M-mode echocardiography.[78] Furthermore, left ventricular mass may be easily derived from parasternal measurements with the following formula:[78]

$$\text{LV mass} = 0.8 * \{1.04[(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]\} + 0.6g$$

Clinical impact

The possible influence of sex and age should be taken into account in the interpretation of the results. Chien *et al.*[79] underlined the importance of LVH as a predictor of cardiovascular risk burden of young persons, by considering 523 boys and 555 girls, aged 12–15 years. They demonstrated a significant positive correlation between left ventricular mass and age; furthermore, age and BMI were the most important determinants of echocardiographic left ventricular mass in young adolescents.[79] In parallel with a progressive increase in left ventricular mass, ageing is also associated with a transition towards a significant increase in relative wall thickness,[80] an independent predictor of cardiovascular events.[81,82] Therefore, age alters normal geometry of the left ventricle (LV) and the normal pattern of ventricular contractility. Dyssynchrony, in fact, could be the natural evolution of the complex interaction between age and ventricular tissue abnormalities.[83] Even considering 30- to 50-year-old patients with low short-term risk for CVD, a high lifetime predicted risk of CVD is associated with concentric left ventricular hypertrophy.[82] In the end, LVH can be considered as a marker of metabolic and hemodynamic changes leading to atherosclerotic disease. Hypertension, ischemic heart disease, kidney disease and other conditions related to the atherosclerotic process could affect left ventricular mass with increasing age, as suggested by the evidence of a relationship between LVH and CCA-IMT[84] and/or carotid plaques. Interestingly, sex also seems to exert a relevant influence on left ventricular structural and functional properties:[85,86] LVH prevalence and left ventricular concentric geometry are greater in women than in men with progressive ageing. In the Framingham population,[85] the prevalence of echocardiographically detected LVH increased dramatically with age, and in particularly in women. The prevalence of LVH was more common in young men, whereas in older individuals, a higher prevalence of LVH in women was observed (from 4.6% in <30 years old to 49% in >70 years old).

De Simone *et al.*[87] reported a significant contribution of adipose mass and waist-to-hip ratio to variability of left ventricular mass in women but not in men. The LIFE study[88,89] suggested that the presence of LVH may be associated with a greater increase in cardiovascular risk in women than in men. Therefore, the differences in LVH regression, together with the greater prevalence of LVH, might contribute to the explanation of the steeper increase in the risk of cardiovascular events with ageing in hypertensive women.[90]

Arterial stiffness

Arterial wall stiffness, an independent risk factor for cardiovascular events, is evaluated by several methods.[91] Pulse wave analysis[92,93] allows the estimation of indices of global arterial stiffness and central (aortic) pressures. In case of stiffer arteries, pulse wave velocity (PWV) is increased and an earlier return of the reflected wave increases systolic pressure. The 'augmentation index', that is the difference between the second and first systolic peaks, expressed as a percentage of the pulse pressure, may be taken as a rough measure of global arterial stiffness. The prognostic significance of augmentation index and central pressures is high,[91,93,94] although normal values for these indices are needed.

Carotid to femoral PWV is the most widely accepted index of arterial stiffness and is currently considered the 'gold standard' for aortic stiffness.[91] It has a predictive value for all-cause and cardiovascular mortality, fatal and nonfatal coronary events, and fatal strokes in different subsets of patients,[91] largely independent from other cardiovascular risk factors, including age and sex.[95]

Implementing rules

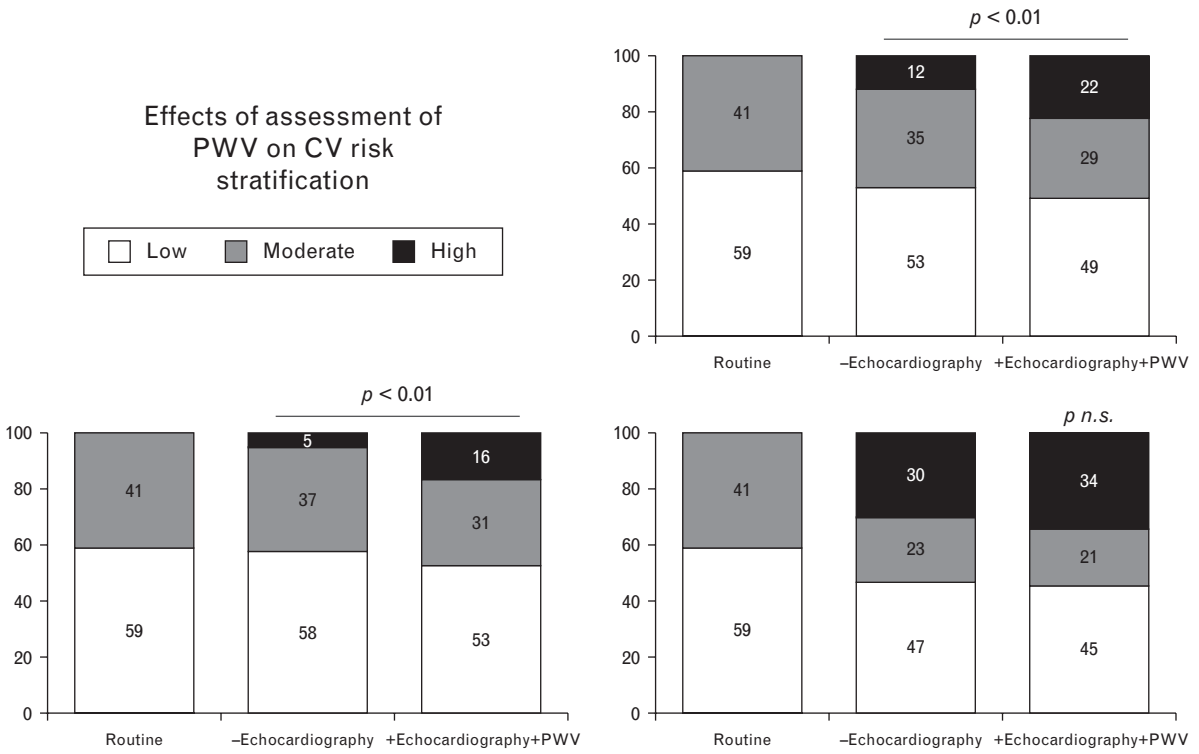
Assessment of PWV is performed by directly measuring the transit time of the pulse wave and the distance between the two sites of measurement; PWV is measured as delta distance/delta time. It is easy and reproducible,[91] although it should be better standardized. Effectively, PWV assessment has undergone several limitations that could impair results of literature studies. For example, the evaluation of peripheral PWV does not resemble the central one because of different responses of systemic vessel wall stiffness to pressure, which could impair evaluations. Heart rate and its regularity could alter the evaluation of this parameter, becoming confounding factors to be considered in the analysis. And, finally, even age and sex could limit the evaluation of PWV.

Clinical impact

Ageing exerts a strong influence on arterial functional properties. In the Asklepios study population,[96] femoral (i.e. muscular artery) stiffness was higher in men than in women. In the same population, carotid (i.e. an elastic artery) stiffness showed a faster increase with age in women than in men. On the contrary, carotid-femoral PWV increased to a similar extent in men and women. A significant difference in mechanical behavior has been observed between elastic arteries at different sites: Paini *et al.*[97] reported that the aorta more rapidly stiffens with ageing than the carotid artery. Ageing exerts a strong influence on arterial mechanical properties. After 50 years of age, there is a linear increase in SBP and a

decline in DBP, thus pulse pressure progressively widens. This is due to the increase in arterial stiffness with ageing. Progressive degeneration of elastin fibres and deposition of collagen play a major role in age-related arterial stiffening; also, the increase in calcium content in the arterial wall, particularly after the fifth decade, might also contribute to the loss of distensibility. The age-related changes in mechanical properties of large arteries are heterogeneous, with a relevant decrease of distensibility only at the level of the more central 'elastic' arteries and much less evident changes in the 'muscular' peripheral arteries. In the wide sample of general population included in the Anglo-Cardiff Collaborative Trial,[98] aortic and brachial PWV, peripheral and central pulse pressure and augmentation index all significantly increased with age. The study showed that augmentation index could be a more sensitive index of stiffening in younger individuals and the PWV in the older ones. Interestingly, no difference between men and women in either aortic or brachial PWV was observed. Augmentation index was significantly correlated with age, and values were higher in women than in men at each decade of life, in line with previous findings indicating increased wave reflection in women. Plantinga *et al.*[99] observed a sex-specific effect of the metabolic syndrome on central augmentation index in a group of hypertensive and normotensive individuals, which was higher in untreated hypertensive women with the metabolic syndrome, a finding in agreement with previous results obtained in treated hypertensive women.[100] On the contrary, in the same group of patients, the metabolic syndrome impaired aortic PWV to a similar extent in both sexes.[99] The impact of age on aortic stiffness is also underlined by the results of a review of the literature published in 2009[101] in which age accounted for 23.5% (from 2.0 to 53.0% in the various studies) of the variance of aortic PWV; among the other factors analysed, BP explained between 1.8 and 41.0% (mean: 13.8%) of variance in aortic PWV, whereas the other factors had only a marginal effect. Of note, normal and reference values for aortic PWV have been recently published.[102] The results have been derived from the Reference Values for Arterial Stiffness Collaboration database, which includes data on 16 867 individuals and patients from 13 different centres across eight European countries.[102] Interestingly, aortic PWV was strongly affected by age and BP, whereas sexual differences in aortic PWV were negligible,[103] even after adjusting for possible confounders. The assessment of aortic PWV may significantly ameliorate cardiovascular risk stratification in addition to other parameters[103] (Fig. 4).

Fig. 4



Effect of assessment of pulse wave velocity on cardiovascular risk stratification. Modified from [103].

Conclusion

Atherosclerosis and its consequences represent an ever present social and health problem all over the world. As previously outlined, physicians are now able to detect the first moments of its development, thanks to new instrumental and noninvasive techniques based, above all, on the adoption of ultrasounds. CCA-IMT, ABI, APAO, brachial artery FMD, LVH and aortic stiffness evaluated by means of PWV are all able to identify early pathological moments of vascular wall changes due to atherosclerosis development. Nevertheless, age and sex could really influence the detection of these parameters. Thus, perception of these confounding factors should be considered by physicians when evaluating early markers of atherosclerosis.

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