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Hypertension and Vascular Dynamics in Men and Women With Metabolic Syndrome

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Metabolic syndrome (MetS), an important component of insulin resistance and cardiovascular (CV) risk, is defined by 3 or more of the following characteristics: abdominal obesity, hyperglycemia, hypertriglyceridemia, and hypo–high-density lipoprotein cholesterolemia. Based on the previously published age- and sex-mediated DESIR (Data from an Epidemiological Study on the Insulin Resistance Syndrome) cohort and parallel central hemodynamic measurements, our goal was to evaluate the effects of MetS on brachial central pulse pressure (PP), PP amplification, aortic stiffness, and wave reflections. These data were then compared with those of patients with essential hypertension but without MetS for the same mean arterial pressure. Increased aortic stiffness, a major mechanical factor predicting CV risk, has been well identified as playing a role in MetS. Its age progression is proportional to the number of risk factors involved in MetS and is responsible for increased systolic blood pressure and decreased diastolic blood pressure with increasing age, the principal hallmarks of hypertension in the elderly. Beyond brachial pressure measurements, central hemodynamic parameters involve increased aortic stiffness, reduced wave reflections, and increased PP amplification, a parameter commonly associated with increased heart rate. With the exception of arterial stiffness, all these findings are opposite in direction to those observed in essential hypertension, in which MetS is absent. A divergent behavior of wave reflections and PP amplification, but not of arterial stiffness, is observed when hypertension is studied alone or when compared with MetS for the same mean arterial pressure. This pulsatile hemodynamic abnormality contributes independently to increase age- and sex-mediated CV risk, justifying new research regarding Framingham scores and drug treatment. (J Am Coll Cardiol 2013;61:12–9) © 2013 by the American College of Cardiology Foundation

Effective cardiovascular (CV) disease prevention requires that multiple risk factors be addressed simultaneously to obtain the most significant reduction of morbidity and mortality in a given population. The combined treatment of type 2 diabetes mellitus and hypertension is an important example of this postulate. About 50% of patients with diabetes have hypertension and 20% of hypertensive patients have diabetes mellitus. To obtain effective CV disease prevention, it is necessary to demonstrate that the combination of antihypertensive and antidiabetic therapy can reduce morbidity and mortality at a level equal to or greater than the sum of each risk factor treated independently. However, this belief has not been regularly observed in clinical practice.

In the double-blind ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure–controlled study (1), a total of 4,733 patients with diabetes and hypertension were divided into 2 groups to reach 2 separate and different brachial systolic blood pressure (SBP) objectives (120 or 140 mm Hg). The final result showed that, irrespective of the SBP level achieved, the same degree of reduction of major cardiac and cerebral vascular risk was observed. These findings suggest that the endpoints of drug effectiveness should have to be carefully chosen when therapeutic trials associating the dual goal of diabetes and hypertension treatments are performed.

Epidemiological studies in hypertension and diabetes mellitus have shown that factors other than high blood pressure play a role in the mechanism of CV morbidity and mortality (2–4). These factors include increased arterial stiffness, disturbed wave reflections, and altered SBP and/or

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pulse pressure (PP) amplification. Thus, with drug treatment, it is important to ask 3 questions: Is arterial stiffness decreased? Are wave reflections modified? Most importantly, does peripheral (brachial) PP remain higher than central PP, as is normally observed (3)? The role of each of these variables has been previously investigated in numerous epidemiological, clinical, and experimental studies. However, answers to these questions are not available associating both hypertension and diabetes mellitus. Furthermore, the roles of age and sex in such populations have not been shown to be related to arterial stiffness and wave reflections.

The purpose of the current report was to determine the possible contribution of aortic stiffness, wave reflections, and PP amplification to the mechanisms of CV complications observed in patients with hypertension, diabetes mellitus, or their combination. In this review, data are provided mainly from a French research project (DESIR [Data from an Epidemiological Study on the Insulin Resistance syndrome]) (5–7). In this investigation, the metabolic syndrome (MetS) is initially analyzed on the basis of age, sex, and brachial artery blood pressure (mainly brachial artery PP). The roles of age, sex, and mostly central (carotid) PP are then investigated in combination with aortic stiffness, wave reflections, and PP amplification. For simplicity, these parameters are shown in Figure 1 and further detailed in this review. Their interrelation was studied to clarify the pathophysiology of MetS and its attendant CV risk. The resulting clinical perspectives are discussed in the last part of this review.

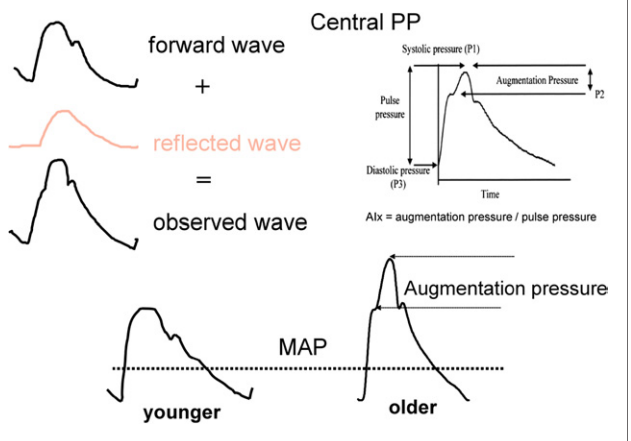

Figure 1 Schematic Representations of the BP Curve

Upper left: the summation of a forward and a backward wave is responsible for the total blood pressure (BP) curve. **Upper right:** a schematic representation of the aortic BP curve with the definitions of augmentation index (AIx) and augmentation pressure. **Lower half:** the same mean arterial pressure (MAP) may correspond to different BP curves in younger **(left)** and older **(right)** patients. However, the cross-sectional areas located under each curve remain equal.

Brachial Blood Pressure, Age, Sex, and the DESIR Study

Basic findings in CV epidemiology. In the past, Richardson et al. (8), and Franklin et al. (9) more recently, provided the first descriptions of the progressive and chronic change of brachial blood pressure as a function of the aging process. Brachial SBP has been shown to increase markedly and exponentially with age. Diastolic blood pressure (DBP) also increases significantly with age, but at patient age 55 years, it declines, even without drug treatment. The more recent French cohort DESIR used a similar design based on brachial artery blood pressure measurements but was focused almost exclusively on the subject of insulin resistance, its pathophysiology, and genetic components. DESIR is composed of 4,293 nondiabetic and diabetic (type 2) men and women age 30 years, all enrolled as volunteers by the French Social Security System. Participants of the cohort have been followed up every 3 years for a total of 9 years on a normal sodium diet, which permits the assessment of the long-term relationships between brachial artery blood pressure and age (10,11). First, the mean values of SBP and DBP, and calculated mean arterial pressure (MAP) and PP, were plotted in successive age groups and evaluated separately in men and women (Fig. 2). These plots are similar to those drawn in previous epidemiological studies. Second, in a departure from the usual description of SBP, DBP, or PP versus age, our subsequent studies (10,11) described the rate of changes of SBP, DBP, or PP versus age. The annual changes of these parameters were then plotted for both men and women, as a function of age at study entry (Fig. 3).

Brachial artery blood pressure and age in DESIR. Figure 2 represents the usual linear relationship of brachial SBP with age and the slightly curvilinear relationship of DBP with age. The same plot may be observed for MAP.

Because MAP is the product of vascular resistance and cardiac output and because cardiac output remains within the normal range in hypertensive and diabetic patients, MAP is an indirect marker of the changes in the resistance component of blood pressure with age. Figure 3 illustrates that while the annual change of SBP increases linearly and continuously with age, the annual change of DBP initially increases with age and then begins to decline with age as early as 45 years. The simultaneous annual increasing change of SBP and decreasing change of DBP with age clearly indicates a progressive reduction of arterial distensibility with age, starting around age 45 years. From the earlier results of Richardson et al. (8) and Franklin et al. (9), the mean value of DBP began to decline over 55 years of age

Abbreviations and Acronyms

AIx = augmentation index
CV = cardiovascular
DBP = diastolic blood pressure
MAP = mean arterial pressure
MetS = metabolic syndrome
NCEP = National Cholesterol Education Program–Adult
PP = pulse pressure
PWV = pulse wave velocity
SBP = systolic blood pressure

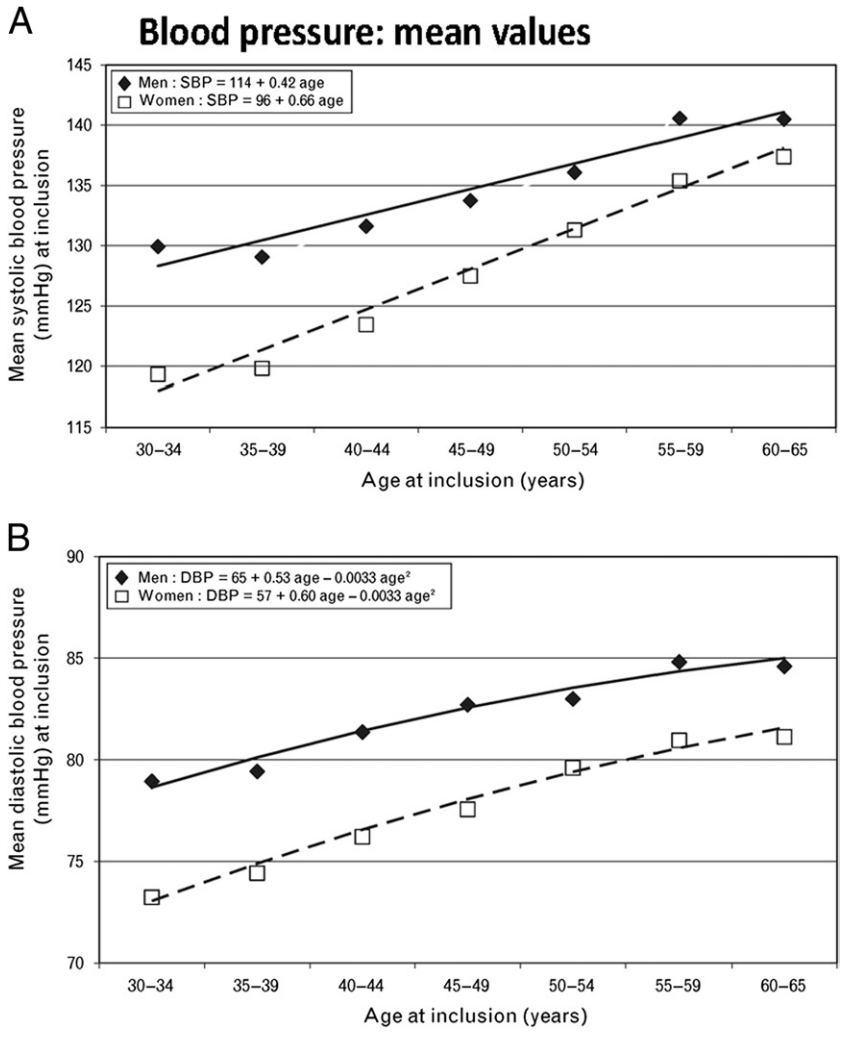

Figure 2 The DESIR Study: SBP and DBP

Relationships between age and **(A)** systolic blood pressure (SBP) and **(B)** diastolic blood pressure (DBP) in men and women. Note that the relations are constantly positive and linear (10,11). DESIR = Data from an Epidemiological Study on the Insulin Resistance Syndrome.

but in the DESIR study, the annual decline of the change in DBP with age occurred much earlier.

Brachial pulse pressure and MetS in DESIR. In this report, the presence of MetS has been defined according to the National Cholesterol Education Program–Adult (NCEP) criteria (5). The NCEP criteria are characterized by 3 or more of the following characteristics: waist circumference >102/88 cm, men/women; fasting glucose >6.1 mmol/l or presence of diabetic treatment; SBP >130 mm Hg and/or DBP >85 mm Hg; triglycerides >1.69 mmol/l; and high-density lipoprotein cholesterol <1.04/1.29 mmol/l, men/women. It is worth noting that in the NCEP definition, only brachial SBP and DBP are considered but not central blood pressure.

When expressed as mean values (Fig. 4), patients with MetS have a significantly higher brachial PP than those without MetS even if their number was relatively small (83 men and 34 women) (11). Increased PP was observed both in men and women and increased exponentially with age in patients with MetS, mainly due to changes in the intercept of the curves. However, only in patients with MetS were the mean values of PP significantly higher in women than in men. Finally, in DESIR, the 2 populations with and without MetS exhibited a significant sex-interaction regarding 4 different parameters: brachial SBP and PP, body weight, and waist circumference. All these findings indicate that the classification of MetS is complex and that sex plays an important interactive role.

Central Hemodynamics, Age, Sex, and MetS

Central hemodynamic parameters. Investigations have been performed in Paris, in a population distinct from that of DESIR and studied in Hotel-Dieu Hospital, during a

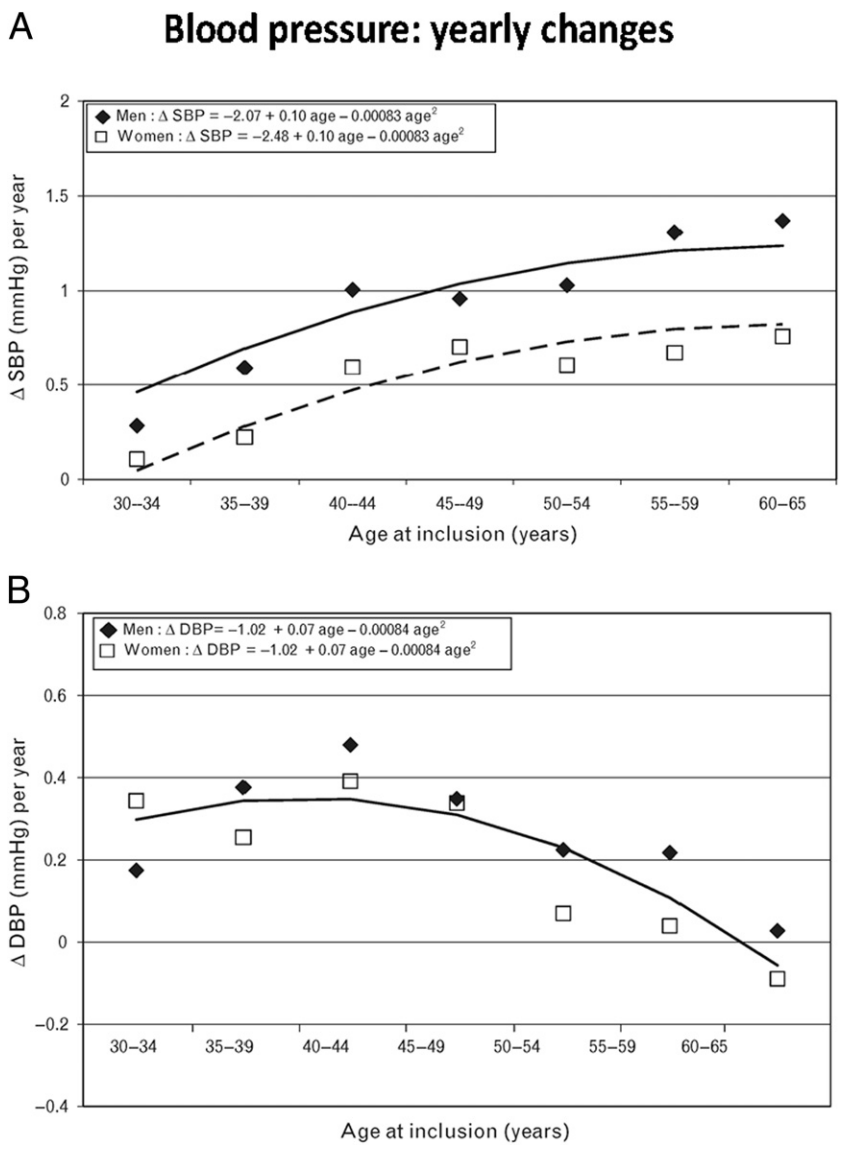

Figure 3 **DESIR Study: Yearly Changes in SBP and DBP**

Yearly changes **(Δ)** between age and **(A)** SBP or **(B)** DBP in men and women (10,11). Note that the relation is positive for SBP and negative for DBP after age 45 years. For DBP, the relation is identical in men and women. Abbreviations as in Figure 2.

1-day hospitalization. Methods have been described in detail elsewhere (4,11,12) and include 613 measurements of carotid–femoral pulse wave velocity (PWV), central and brachial artery parameters, and study of wave reflections through augmentation index (AIx) measurements, all performed after drug adjustment if necessary (Fig. 1). Compared with patients without diabetes mellitus, patients with diabetes mellitus have, for the same age, sex, and MAP, significantly higher mean values of heart rate, aortic stiffness, and PP amplification but lower mean values of AIx. Figure 5 (11,13) provides a summary of the main results and also indicates the corresponding definitions of brachial and central PP measurements and their ratio.

Aortic stiffness. After ventricular contraction, the pressure pulse generated by the heart travels along the aorta as a wave. The velocity of propagation of this wave (i.e., PWV) may be calculated from the arrival time and the distance between applanated pulses located at 2 different sites in the arterial tree, such as the carotid and the femoral arteries. Because a fundamental principle states that pulse waves travel faster in stiffer arteries, PWV measurement is considered the best surrogate for the evaluation of aortic stiffness. Its value in the aorta is approximately 5 m/s in young persons at rest but increases with age. Aortic PWV is a strong and independent predictor of overall risk and CV risk in hypertension and diabetes mellitus, particularly in the

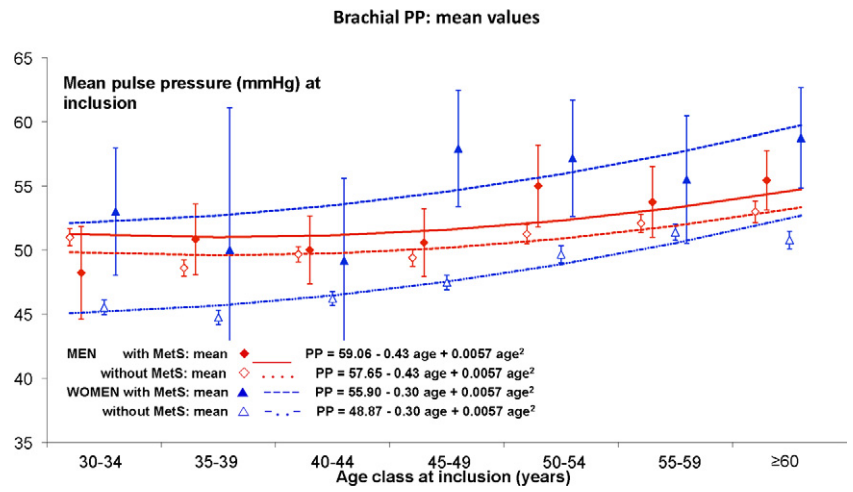

Figure 4 **Brachial PP**

Mean values versus age in men and women with and without metabolic syndrome (MetS) (10,11). PP = pulse pressure.

elderly (14,15). PWV increases in MetS in proportion to the number of MetS criteria and increases with age more rapidly in patients with MetS than in patients without MetS for the same MAP (10,11,13,16). In MetS, PWV is associated with increased values of carotid wall thickness and subcutaneous trunk fat but not of carotid plaques or major change of upper limb PWV (4).

Wave reflections. Small vessels and arterioles are the principal sites of wave reflections from the incident wave, and the reflected waves return from the periphery to the larger thoracic aorta at the same PWV (Fig. 1). Insulin has significant vasoactive properties, acting independently of the heart on these resistive vessels and precapillary arterioles located in muscular and fat tissue. Westerbacka et al. (17) have shown that, in addition to insulin's arteriolar effect, it acts on large arterial vessels through the mechanism of wave reflections, causing a reduction in amplitude and/or timing of the carotid pulse under conditions of euglycemic clamp.

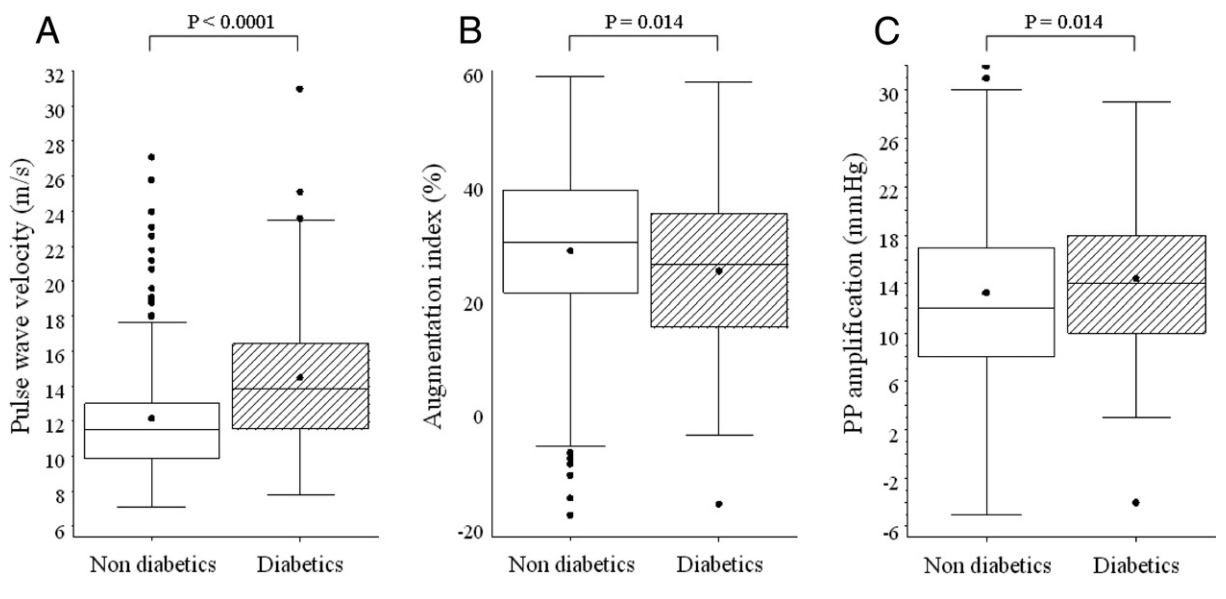

Figure 5 **Summary of Main Results**

Difference in **(A)** pulse wave velocity, **(B)** augmentation index, and **(C)** pulse pressure (PP) amplification in diabetic (n = 126) versus nondiabetic (n = 203) patients. A similar finding is observed in patients with and without metabolic syndrome. Amplification = central/brachial PP. p Values are adjusted for age, sex, and mean arterial pressure (11,13).

In patients with insulin resistance, particularly in those with MetS, this physiological mechanism is disrupted and may contribute to the development of systolic hypertension. Obviously, the associated roles of endothelin, angiotensin, or oxidant stress to insulin cannot be excluded from this simplified description.

PP amplification. The pressure wave changes shape as it travels down the aorta, such that the blood pressure values are not identical when measurements are made simultaneously at different points (Fig. 1). Whereas SBP and PP actually rise with distance from the heart, DBP and MAP fall very slightly (about 2 mm Hg) over the same aortic course (3). Thus, the pressure oscillation amplitude between systole and diastole, represented by central PP, nearly doubles in the periphery (18,19). This pulse amplification is a result of the arterial stiffness gradient and diameter narrowing along the arterial tree. It is related to the timing interaction of the forward ejected and backward reflected pressure waves at each site of the arterial tree (Fig. 1). Late synchronization (e.g., at the ascending aorta) of the 2 waves leads to lower SBP than early synchronization (e.g., at the descending aorta) for the same MAP (3). Of note, this timing is highly affected by variations in heart rate (20,21).

The SBP and PP amplification are physiological findings, which approximate 14 mm Hg between the thoracic aortic root and the brachial artery, and continue into aortic ramifications out to about the third-generation level of branches. AIx is the increase in SBP and PP produced by the reflected wave and expressed as a percentage of the PP (Fig. 1). It can be measured from the applanated carotid pulse and offers a clinical means for assessing the magnitude of central pressure and wave reflections. The lower the central AIx, the greater the amplification. Amplification keeps the central SBP and PP low and protects the heart against an increase in post-load, but amplification is markedly reduced with increasing age. Disappearance of amplification is associated with increased amplitude of the central reflected wave, contributes to increases in the left ventricular systolic burden, decreases the late systolic ejection flow velocity (22), and is a significant predictor of CV risk (3,20).

Heart rate. Because heart rate is increased in MetS, the question is whether high heart rate or wave reflections or both are major mechanisms accounting for higher amplification in this insulin-resistant state. In a cross-sectional study, we have already shown that PP amplification, HR, and PWV, but not AIx, are increased in patients with MetS compared with control patients without MetS but with the same age, sex, and MAP (18,19). Conversely, the possibility of an altered ventricular ejection with relatively slower flow velocity in late systole is also important to consider (22). However, our results showed that the difference in carotid–brachial PP amplification between patients with and without MetS disappears after adjustment for both heart rate and PWV. AIx (Fig. 1), the main clinical index permitting evaluation of wave reflections in clinical practice, was shown to be the principal predictor of PP amplification. Although the 2 parameters are inversely related, our results indicate that AIx represented significantly different contributions (28% vs. 19%) to the amplification total variance in patients without and with MetS (18,19).

MetS and the Role of Vascular Factors in the Assessment of CV Risk

Previously, CV physiologists found that the pulsatile BP curve was better described when divided into 2 components: a steady component (MAP) and a pulsatile component (PP) (21,23). At a given cardiac function, the nonpulsatile component relates to the status of small arteries (i.e., systemic vascular resistance). Conversely, PP that corresponds to the pulsatile flow ejected by the heart is influenced by 2 distinct parameters of the arterial system: stiffness and wave reflections. Early epidemiological studies have indicated that, in terms of hazard ratio, MAP best predicts overall CV risk (brain, heart, and kidney), whereas PP best predicts coronary risk (23). Such findings show that a new conceptual approach is necessary to the understanding of vascular factors in MetS.

Within the microvascular network (24), MetS involves structural changes of arterioles and capillary rarefaction that in turn are associated with an increase in vascular resistance and a resultant increase in MAP. Within the macrocirculation (25), a similar process of vascular remodeling occurs and increases arterial stiffness, which favors an increase in SBP but also a decrease in DBP. Finally, in MetS, DBP level is the result of 2 mechanisms, an increase of systemic vascular resistance, which tends to increase DBP, and an increase of arterial stiffness, which is associated with low DBP. Taken together, all these factors cause an increase in PP, which, at the level of the central arteries, may be counterbalanced by the presence of increased heart rate and blunted wave reflections. Finally, differences in the sexes might also contribute to accentuation of the role of PP (19).

The circulatory differences between men and women can be summarized as either hormonal or nonhormonal. Before menopause, high estrogen levels induce vascular relaxation through their influence on vascular cell membranes, endothelium, and smooth muscle (26). These effects lead to increased distensibility of the carotid arteries and aorta. With menopause, the reduction in estrogen levels and their associated effects help explain the accelerated CV risks in women when compared with men of the same age. The nonhormonal gender differences, however, are lifelong and even more important to consider than hormonal factors. They relate to lower body height and size with higher heart rates and lower cardiac outputs in women. Women's shorter stature and shorter length of the arterial tree might be responsible for their faster heart rate, an acceptable interpretation of their particular biological properties (27). Shorter stature places the arterial pulse reflecting sites closer to the heart and, at the same PWV, brings the reflected wave back into the central aorta earlier in systole with the

resultant decrease in pulse amplification and AIx. Lower cardiac output, lower stroke volume, and smaller arterial diameters are lifelong differences, with their possible consequences on the central aorta. Finally, when the association between diabetes and hypertension is considered, it seems logical to study PP in men and women separately.

An important consequence of MetS is a progressive and early inability of the peripheral vascular networks to adequately perfuse skeletal muscle during periods of elevated metabolic activity. Resulting consequences involve endothelial dysfunction, oxidative stress, and inflammation. Several features of MetS are characterized by increased production of reactive oxygen species and nitrogen species and subsequent oxidative stress. Antioxidants may limit the oxidative process by inactivation of free radicals and could protect patients from MetS-related complications. However, data from a French randomized controlled trial failed to demonstrate an effect of supplementation with multiple antioxidants on MetS risk (28). This finding is in line with most other primary and secondary prevention trials that found no beneficial effect of antioxidant supplementation on classical CV risk factors (29). This lack of benefit may be a simple reflection of the underlying association with differences in overall dietary patterns. Hercberg et al. (30) investigated the association between dietary patterns and PWV measured 7.5 years after the beginning of the diet. The authors observed a positive correlation between a diet high in alcohol and meat, and an inverse correlation with diets that included fiber, vitamins B_9 and C, beta-carotene, and calcium. These findings suggest a role for diet in the stiffening of large arteries in participants free of known CV disease.

Conclusion and Prospective Views

This review has shown that the management of hypertension may differ markedly in the presence or absence of associated diabetes mellitus and/or MetS. This difference relates not only to arterial stiffness but also to changes in other pulsatile hemodynamics such as wave reflections, PP amplification, and heart rate. Based on multiple regression analysis, PWV, wave reflections, and PP amplification are all influenced by age, sex, heart rate, and MAP. They are also influenced by several glucose-related factors such as waist circumference. All these factors play a consistent role in blood pressure control when hypertension and diabetes are associated. Thus, new therapeutic designs should be proposed for patients with hypertension and MetS and/or diabetes mellitus. First, the choice of medications causing aortic destiffening should be discussed, such as those involving angiotensin blockade, calcium inhibition, and/or diuretics (31). Second, the specific indications of drugs causing bradycardia should be reviewed, particularly in patients with diabetes. Third, lifestyle modifications might be recommended, mainly in the fields of nutrition (32). Finally, the links of hypoglycemic agents and insulin with arterial stiffness and wave reflections need to be more firmly established.

In patients with hypertension, whether or not associated with diabetes, the principal recommendation for drug treatment is to reduce SBP (<130 or 140 mm Hg) and DBP (<80 or 90 mm Hg). This recommendation agrees with traditional aspects of CV epidemiology, which highlight the role of both elevated SBP and DBP as dominant vascular factors acting on CV risk (4). However, CV epidemiology now indicates that arterial stiffness is another independent factor to consider in the reduction of CV risk and Framingham scores (19,33). In the context of the combination of hypertension and diabetes, the presence of increased arterial stiffness requires the reduction of SBP but also the need to maintain and/or even increase DBP. Although counterintuitive, low DBP is alone a significant risk factor for cardiac complications, particularly in the elderly. Finally, in the context of treatment of hypertension associated with diabetes, we suggest that experts working in both fields should critically review therapeutic recommendations. CV risk is usually assessed by using Framingham scores, which involve a number of metabolic factors but only SBP and DBP as mechanical factors. Research by Mitchell et al. (34) has shown that, in patients assessed after a first CV event, the introduction of PWV into the panel of the Framingham score may significantly improve the quantification of CV risk. CV risk assessment could be further improved if wave reflection and PP amplification were also taken into account in patients who have both hypertension and diabetes mellitus.

Units of tables and figures may differ from each other since the form in their original publication has been retained; see text.

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Key Words: arterial stiffness ■ hypertension ■ metabolic syndrome.