Arterial Stiffness, Pulse Pressure, and the Kidney

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Classical studies indicate that the contribution of kidneys to hypertension is almost exclusively related to the association between mean arterial pressure (MAP) and vascular resistance. Recent reports including estimates of glomerular filtration rate (GFR) have shown that pulse pressure (PP) and pulse wave velocity, 2 major indices of arterial stiffness, now emerge as significant predictors of cardiovascular risk and age-associated decline in GFR. Such findings are mainly observed in patients with hypertension and renal failure and in atherosclerotic subjects undergoing coronary angiography. In such patients, amplification of PP between ascending and terminal aorta at the renal site is constantly increased over 10 mm Hg (P < 0.001), whereas MAP level remains continuously unmodified. This PP amplification is significantly associated with presence of proteinuria. Furthermore, increases in plasma creatinine and aortic stiffness are independently and positively correlated (P < 0.001) both in cross-sectional and longitudinal studies. All these relationships associating PP, arterial stiffness, and renal function are mainly observed in patients 60 years of age or older. Furthermore, in renal transplant patients and their donors, subjects have been recruited for evaluations of arterial stiffness and posttransplant decline in GFR. Determinants of GFR decline were evaluated 1 and 9 years after transplantation. The first year GFR decline was related to smoking and acute rejection, whereas the later was significantly and exclusively associated with donor age and aortic stiffness. Thus, in hypertensive humans, the observed association between PP and GFR suggests that the 2 parameters are substantially mediated by arterial stiffness, not exclusively by vascular resistance.

Keywords: arterial stiffness; blood pressure; hypertension; pulse pressure and the kidney.

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There are 2 hemodynamic components of pressure and flow: a steady component and a pulsatile component.1 The former is represented by mean arterial pressure (MAP), the product of cardiac output by vascular resistance, a classical index of the “caliber” of small arteries, which is usually considered as the principal hallmark of subjects with hypertension. The latter is represented by pulse pressure (PP), which is determined by stroke volume, aortic stiffness, and wave reflections. Aortic stiffness and wave reflections, but not stroke volume, are determined by the ability of large arteries to change the cyclic flow coming from the heart into a continuous flow at the peripheral level, thus enabling to optimize the oxygenation of tissues. While MAP is the principal marker of small arteries alterations, PP is mainly related to the status of large arteries. However, both factors may contribute substantially to the mechanisms of hypertension. In the recent years, the distinction between the conduit (MAP) and buffering (PP) functions of large arteries became of paramount importance when these 2 distinct properties were shown to represent 2 independent predictors of cardiovascular (CV) risk.2 While MAP predicts together cerebral, renal, and cardiovascular risk, PP predicts more selectively heart and kidney risks, a point which is important to focus in detail in this report.

The purpose of this review is to describe the principal characteristics of PP and to indicate under which conditions MAP and PP significantly differ. In fact, both are necessary to the pathophysiology of hypertension, particularly regarding their respective role on the kidney structure and function. This aspect is particularly investigated in this review.

BASIC CONCEPTS

Following ventricular contraction, the pressure pulse generated by the heart travels along the aorta as a wave. It is possible to calculate the velocity of propagation of this wave (i.e., pulse wave velocity (PWV)) along the aorta from the interval between 2 blood pressure (BP) curves located at 2 different sites in the arterial tree. Because the fundamental principle is that pulse waves travel faster in stiffer arteries, PWV measurement is considered the best surrogate to evaluate carotid–femoral arterial stiffness, a parameter not involving here brachial–ankle measurements. The value of carotid–femoral stiffness is 3–5 m/s in young persons at rest but increases considerably with age. Given that peripheral arteries are markedly stiffer than central arteries, an

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The intimal thickening is composed of several elements, including collagen and elastic fibers and also myofibroblasts that have migrated in from the media. These myofibroblasts are aligned in the long axis of the lumen (as opposed to the circumferential arrangement of medial myocytes). Hence, their contraction would have little effect on lumen caliber development of increasing aortic stiffness (high PWV) and altered wave reflections with aging and hypertension completely abolishes the differences between central and peripheral PP by age 50–60 years, with major consequences for ventricular load and coronary perfusion. The increased aortic PWV means that the reflected waves return to the aortic root earlier, during late systole so that aortic PWV is superior or equal to peripheral PWV. In this situation, the reflected waves combine with the forward-traveling wave to create an increased “augmentation” of the central SBP and ventricular load. Furthermore, because the backward pressure returns in systole, and not in diastole, as a consequence of enhanced PWV, DBP and coronary blood flow tend to be reduced, a situation favoring coronary ischemia. Finally, the classical phenotype of systolic hypertension in the elderly is achieved and mainly characterized by an increased PP.

Under all these specific conditions, it is evident that the potential relationships between the kidney (with or without terminal uremia) and the mechanical properties of the large arteries, arterial stiffness and PP, have been insufficiently investigated in the recent years, as well in animal and in human models of hypertension. Thus, the main purpose of the present study is: first, to define the methodological aspects enabling to characterize the simultaneous changes observed in arterial and renal structure and function in men and women; second, to explore, in specific clinical investigations, the cross-sectional relationships between arterial function and glomerular filtration rate (GFR) in patients with renal failure and/or atherosclerotic coronary disease; third, to describe the principal time-dependent relationships between large arteries and glomerular structure and function, particularly those noticed under drug treatment; and, finally, fourth, to investigate the arterial kidney function system under renal graft. From such observations, perspectives on the role of arterial stiffness and PP in the equilibrium of renal microcircular network are important to characterize in subjects with human hypertension.

**METHODOLOGICAL PROBLEMS ASSOCIATING GLOMERULAR AND VASCULAR ALTERATIONS**

**Arterial stiffening**

In all aging individuals, there is a progressive breakdown in elastic fibers in the aorta and large elastic arteries, with the result that: PWV increases, PP rises, and flow becomes pulsatile further down into the ramifications of the arterial tree. In the kidney parenchyma, supplied by muscular arteries and arterioles, there is a progressive intimal thickening, as a part of the normal aging process. This thickening is greater on average among Blacks than Whites and has a strong correlation with hypertension.

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Glomerular alterations

Nowadays, numerous data suggest that there are 2 different processes leading to glomerulosclerosis: ischemia and loss of renal autoregulation. Arterial stiffening with increased PP down as far as the afferent arteriolar level likely plays an important role in the progression of glomerular lesions and so is important to consider. Loss of renal autoregulation with glomerular hypertrophy, hyperfiltration, and focal segmental glomerular sclerosis may ensue and contribute significantly to nephrosclerosis, particularly in the Black population. Ischemic glomerular sclerosis, however, may ultimately be the most important issue of arterial-glomerular alterations, with consequent hypoxia in the parenchyma beyond, leading to tubular atrophy and interstitial fibrosis.

The capillaries of the heart and the brain are protected from increased mean and pulsatile BP by the precapillary arterioles, which provide approximately 75% of the resistance of the vascular bed. In contrast, in the kidney, a smaller efferent arteriolar resistance compared with the afferent arteriolar resistance produces a relatively small pressure decrease across afferent glomerular arterioles, and pulsatile pressures in the glomerulus are relatively high, approximating 60% of the arterial values. Although this maintains glomerular filtration, it exposes glomerular capillaries to the potentially damaging effect of PP. Normally, a combination of myogenic tone in the afferent arteriole and tubule-glomerular feedback is largely responsible for the autoregulation of renal blood flow, which is achieved over a wide range of steady values of perfusion pressure, traditionally defined in terms of steady pressure.

However, it is important to note that an increased PP may influence renal hemodynamics in animal or human models in which PP is out of proportion with MAP, because myogenic tone in the afferent arterioles has been shown to be affected by PP. This has been reported in the remnant kidney model in animals, and in humans may be observed with advancing age beyond the fifth decade, providing a possible mechanism for an age-related decline in renal function. On the other hand, it is conceivable that PP-induced increases in afferent arteriolar tone may be offset by tubule-glomerular feedback mechanisms acting through an increase in efferent arteriolar tone or an altered activation of the renin–angiotensin–aldosterone system, or both.

Main aspects of glomerular and arterial hemodynamics

To determine the relationship between arterial function (stiffness and wave reflection) and glomerular hemodynamics, GFR and effective renal plasma flow are usually measured by urinary clearances of 99mTC-DTPA and 131I-hippuran, respectively. Filtration fraction is computed as GFR/effective renal plasma flow. Arterial stiffness is estimated by carotid–femoral PWV. Wave reflections are evaluated by carotid augmentation index, reflection magnitude, and the round-trip travel time of the pressure wave. All these variables suppose, of course, the absence of heart failure in their basic definitions.

Flow velocity waveforms are recorded on the use of 2 different parameters. The first one is based on the study of renal segmental arteries with duplex ultrasound, which are used widely to calculate the resistive index (RI equals: 1 – end-diastolic velocity/peak systolic velocity). The second one is based on the study of femoral arteries, which are used to calculate the reverse/forward flow index and diastolic/systolic forward flow ratio. Considering the conventional view that RI reflects the peripheral vascular resistance, these results would suggest that the aortic PP determines the renal vascular resistance. According to Hashimoto and Ito, we suggest as another potential view that renal RI may partly reflect also the renal flow pulsation. It can be clearly seen from the equation that the RI is, by definition, an evaluation of the arterial flow pulsatility. Indeed, specifically, an increase in RI means a relative increase in systolic flow and a relative decrease in diastolic flow. According to this view, the present results would indicate that the aortic pressure pulsation might also determine the renal flow pulsation and affect PP.

THE STIFFNESS–GFR ASSOCIATION: CLINICAL ASPECTS

Large artery damage in subjects with end-stage renal disease

In patients with end-stage renal disease undergoing hemodialysis, clinical studies have shown that BP values are most frequently characterized by increased SBP alone with normal or even low DBP. Such alterations are consistently associated with increased stiffness of large conduit arteries and early wave reflections. Increased stiffness was shown to be independent of MAP level but largely influenced by the diffusion of large artery calcifications, often related to poorly controlled calcium–phosphate homeostasis. Studies demonstrate that phosphate retention caused by reduced urinary excretion in renal patients is associated with human aortic smooth muscle cell calcification, an early morbid phenomenon that has been recognized as a major factor contributing to large artery stiffness several decades ago. This hemodynamic pattern is associated with vascular remodeling, characterized by dilation of elastic and muscular-type arteries, and increased wall thickness. In end-stage renal disease patients, arterial remodeling and, more importantly, increased arterial stiffness, as measured from PWV, are strong independent predictors of all causes and mainly CV mortality. Moreover, a therapeutic trial in end-stage renal disease patients by Guerin et al. has shown that after long-term BP reduction, CV survival is observed mainly in those patients showing adequate BP and PWV control. However, patients with appropriate BP reduction but who maintain elevated PWV do not survive. This observation
clearly shows the critical deleterious role of increased stiffness on morbid arterial events.

The mechanisms responsible for arterial stiffening in patients undergoing hemodialysis are incompletely understood but are observed in nondiabetic subjects and cannot be exclusively related to standard CV risk factors such as glucose intolerance, hypercholesterolemia, overweight, or increased tobacco consumption.7,13 Furthermore, studies comparing structural and functional alterations of carotid and radial arteries in end-stage renal disease patients have shown that the observed vascular alterations are largely independent of age and of mechanical factors, such as increased local wall stress and high BP. Such findings are observed on central elastic and peripheral muscular arteries. In particular, in vivo studies performed on the radial artery, a blood vessel poorly altered by aging and unmodified by atherosclerosis, have shown that the major mechanism of vascular alterations was characterized by an increased stiffness of the vascular wall matrix, a parameter consistently associated to "uremia" and not to high BP.7,13 Studies in experimental uremia and in vitro in arteries of uremic patients have shown striking structural alterations involving an increase in wall thickness, cross-sectional media, and various components of extracellular matrix including possibly collagen but not elastin. In addition, important calcifications of elastic lamellae are present, suggesting the potential role of parathormone. Such structural changes are not similar to those observed in aging, atherosclerosis, or standard hypertension. Thus, the role of renai factors may be logically proposed, as those related to fluid redistribution, the accumulation of advanced glycosylation end product and/or the accumulation of an endogenous inhibitor of nitric oxide synthesis, and, finally, oxidative stress-related tissue damage.7,13 Nevertheless, whether the stability of large vessels depends on the primary cause of the renal disease or even precedes kidney alterations remains largely ignored and needs to be explored.

Whether arterial stiffness and kidney function are statistically associated in subjects with plasma creatinine below 130 µmol/l has recently been determined in 1,290 subjects. In subjects with normal or elevated BP values and plasma creatinine below 130 µmol/l, subjects were divided into 3 tertiles according to the calculated creatinine clearance.13 From the 1,290 subjects, only the low-tertile group presented a significant negative association between PWV and creatinine clearance independently of BP and standard risk factors. This association was stronger in subjects below 55 years old. Increased stiffness of central arteries was statistically associated with reduced creatinine clearance in subjects with normal or mild-to-moderate renal insufficiency, indicating that kidney alterations may interact not only with small but also large arteries, and that this finding was independent of age and standard risk factors.

Finally, longitudinal studies have provided evidence that, independently of MAP, aortic PWV increases more rapidly with age in subjects treated for hypertension than in untreated normotensive control subjects.14 Furthermore, from all factors known to influence the increase in PWV with age, the most important was shown to be baseline plasma creatinine level.15

To summarize, in normal subjects and in those with high BP, high PWV and reduced creatinine clearance are significantly and independently associated. However, in subjects treated for hypertension, the elevation of PWV with age is steeper in those with higher values of baseline plasma creatinine.

### Atherosclerotic subjects with high coronary risk

BP was measured invasively in the ascending aorta, abdominal aorta (at the level of kidneys), and iliac artery in 101 subjects (mean age: 63 ± 11 years; 61 men) undergoing coronary angiography (Table 1).16 PP was so measured progressively at the same sites along the aorta. Independently of age, sex, and the presence of coronary stenosis, the level of PP amplification at the site of the ascending and the abdominal aorta was 64 and 73 ± 20 mm Hg (P < 0.001), respectively, whereas at the same sites, MAP remained constantly equal to 96 ± 14 mm Hg. This PP amplification did not differ significantly between patients with and without coronary artery stenosis. Irrespective of confounding variables, high PP measured in the ascending aorta and at the level of renal arteries (but not in the iliac artery) was independently related to proteinuria. The increase in PP from the ascending aorta to the renal level was negatively associated with leukocyte count, even after multivariate adjustment (β coefficient: −0.19; 95% confidence intervals: −0.39–0.0; P < 0.05). Increased plasma creatinine and aortic PWV were independently and positively correlated (β coefficient: 0.36; 95% confidence interval: 0.18–0.54; P < 0.001) (Table 2). These findings were observed both in normotensive and

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**Table 1. Intra-arterial blood pressure at different sites (with permission: Temmar et al.**

<table>
<thead>
<tr>
<th>BP parameter</th>
<th>Ascending aorta</th>
<th>Abdominal aorta</th>
<th>Iliac aorta</th>
<th>Adjusted P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>137.7 (24.7)</td>
<td>143.7 (23.3)</td>
<td>145.8 (24.5)</td>
<td>0.154</td>
</tr>
<tr>
<td>DBP</td>
<td>73.5 (11.3)</td>
<td>71.1 (11.2)</td>
<td>70.9 (11.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>MBP</td>
<td>96.0 (14.9)</td>
<td>95.8 (14.3)</td>
<td>96.1 (14.6)</td>
<td>0.534</td>
</tr>
<tr>
<td>PP</td>
<td>64.3 (20.5)</td>
<td>72.5 (19.2)</td>
<td>74.9 (20.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abdominal aortic blood pressure was measured on the level of renal arteries. Values are mean (SD). Abbreviations: BP, blood pressure; CAS, coronary artery stenosis; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

*Adjusted for age, sex, and CAS.

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hypertensive subjects, independently of age, diabetes, and atherosclerosis.

Finally, in various situations involving mostly severe renal or coronary organ damage, a significant relationship between loss in GFR and increase of carotid–femoral arterial stiffness was noticed. Proteinuria is frequently observed. Whether the changes in this parameter may be considered as of steady or pulsatile origin remain yet frequently difficult to assess.

**PP, AGE, AND DRUG TREATMENT**

**PP and age**

The relationship between brachial PP, age, and the renal aging process was primarily studied in a cohort of 212 patients, which were never-treated but were characterized all by isolated systolic hypertension. GFR and effective renal plasma flow were measured using constant infusion of technetium 99m (99mTc)-DTPA and 131I-ortho-iodohippurate, respectively, and timed urine collections. The relationship between brachial PP and renal function was studied using a linear regression model in the total population but including 40–49, 50–59, and 60 years and older age categories (Figure 2). In the whole population, there was an inverse relationship between PP and GFR; however, this relation did not persist after adjustment for age. In fact, the inverse relationship between the 2 variables was only present in patients aged 60 years or older. This relationship in elderly patients remained after adjustment for age, gender, MAP, and CV risk factors (P = 0.006). It was so suggested that PP, a possible marker of arterial stiffening, had a detrimental influence on the age-related decline in GFR, after 60 years of age in patients with never-treated subjects with isolated systolic hypertension.

A longitudinal study (median follow-up period of 5.8 years) was conducted in 132 never-treated patients with essential hypertension investigated at baseline. The effect of treatment on the GFR and effective renal plasma flow, estimated by urinary clearances of isotopic markers, was assessed. Satisfactory control of hypertension (brachial BP < 140/90 mm Hg) was achieved in 57% of the population. During follow-up, the yearly change in the GFR was −1.72 ± 0.21 ml/min per year (mean ± SE of the mean). In univariate regression analysis, the change in the GFR was correlated with baseline PP (r = −0.27, P = 0.002) (Figure 3), whereas no influence of systolic, diastolic, or mean BP, as well as baseline albuminuria or left ventricular mass index, was found. Multivariate logistic regression analysis showed that only baseline PP conveyed a significant odds ratio of

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>95% CI</th>
<th>Partial R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine</td>
<td>0.36</td>
<td>0.18–0.54</td>
<td>0.14</td>
</tr>
<tr>
<td>Age</td>
<td>0.36</td>
<td>0.17–0.54</td>
<td>0.15</td>
</tr>
<tr>
<td>MBP</td>
<td>0.20</td>
<td>0.02–0.38</td>
<td>0.07</td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>−0.20</td>
<td>−0.38 to −0.02</td>
<td>0.13</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−0.20</td>
<td>−0.38 to −0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>Diabetes (yes: 1; no: 0)</td>
<td>0.17</td>
<td>0.00–0.35</td>
<td>0.07, 0.52</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MBP, mean blood pressure; PWV, pulse wave velocity; RAS, renin–angiotensin system.
accelerated decline of GFR (>median of 1.5 ml/min per year), independently of age, baseline GFR, MAP, and other known CV risk factors. No influence of the type of antihypertensive treatment (64% of the population had received angiotensin-converting enzyme inhibitor) was detected. PP (a marker of arterial stiffening in the absence of heart failure) was again suggested as an independent determinant of the treatment-associated decline in renal function in essential hypertension. No influence of target organ damage (albuminuria or left ventricular hypertrophy) was detected.

**PP, arterial stiffness, and drug treatment**

The influence of different antihypertensive drug classes on improving arterial stiffness beyond BP reduction is not widely available. In a recent study, the aim was to determine whether the artery stiffness can be improved because of antihypertensive treatment but independently of BP lowering. A meta-analysis of individual data from 15 randomized, controlled, and double-blind parallel-group trials was so performed in France between 1987 and 1994. The primary endpoint was the changes of carotid–femoral PWV after treatment in 294 patients with mild-to-moderate essential hypertension all previously untreated. Treatments tested were placebo (n = 88), angiotensin-converting enzyme inhibitors (n = 75), calcium antagonists (n = 75), beta-blockers (n = 30), and diuretics (n = 26). In the short- and long-term trials, PWV decreased significantly by −0.75 and −1.3 m/s in the active treatment group compared with by +0.17 and −0.44 m/s in the placebo group, respectively. Active treatment was independently related to the changes in PWV and explained 5% and 4% of the variance in the short- and long-term trials, respectively. In the short-term trials, angiotensin-converting enzyme inhibitors were more effective than calcium antagonists and placebo on improving arterial stiffness. In the long-term trials, angiotensin-converting enzyme inhibitor, calcium antagonists, beta-blocker, and diuretic reduced significantly PWV compared to placebo. The study clearly showed that antihypertensive treatments improved the arterial stiffness beyond their effect on BP.

**PP and kidney transplantation**

In subjects with renal disease, reduced renal function and increased arterial stiffness are significantly associated in cross-sectional studies. The relationship is independent of age, BP, and atherosclerosis. Because both variables are independent predictors of CV risk, time-dependent relationships between them are important to evaluate.

Aortic PWV was measured noninvasively by comparison with healthy volunteers in 101 living kidney donors and their 101 corresponding recipients. Healthy volunteers were divided into 2 groups: one was recipient related (RR) through familial links and the other was non-RR. Independently of age, gender, and BP, PWV was significantly elevated in donors and recipients by comparison with the 2 groups of healthy volunteers, called RR and non-RR. PWV was significantly higher in the RR than in the non-RR group (Figure 4). While in healthy volunteers, PWV was exclusively related to age, gender, and BP; in donors and recipients, this parameter was rather associated with a cluster of CV risk factors, including smoking habits and plasma glucose.

The major factors related to PWV were of renal origin, including: time dependence since nephrectomy (donation date) in donors and renal rejection in recipients. Finally, plasma creatinine doubling secondary to chronic allograft nephropathy was significantly associated both to renal rejection and donor PWV, independently of age.

In kidney diseases, renal function decreases over time as a result of reduction in the number of functioning nephrons with age. However, till the recent years, this decline has been poorly studied in recipients and living donors in relation to the alterations in PWV parameters. Renal transplant patients and their living donors were recently recruited for evaluation of aortic stiffness and determination of the post-transplant trends in renal function using the adjusted classical Cockcroft-Gault formula. Renal function decline was expressed as the yearly loss of estimated GFR in ml/min/1.73 m². Determinants of filtration rate decline were evaluated in recipients at 1 year and at a mean of 9.2 ± 3.5 years after transplantation (Table 3). The first year decline was related to smoking and acute rejection. Later decline in recipients was significantly associated with donor age and aortic PWV. These findings clearly indicate that, in the long term,
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significant associations affecting donor and receiver may be established during renal transplantation. At the same period, a mediating role of PP and arterial stiffness is noted, and, at a same time, a significant association with urinary phosphate excretion. Finally, when analyzed all together, our results in renal transplants confirm the presence of important relationships between PP, arterial stiffness, and the kidney.

CONCLUSION AND PERSPECTIVES

Till the recent years, the pathophysiological role of the kidney in the mechanisms of hypertension has been based almost exclusively on the concept of MAP and vascular resistance. In American Journal of Hypertension, 589 publications are indicated in PubMed by the terms associating “hypertension and kidney structure and function” and 136 of them refer specifically to the calculation of MAP. The most important of these publications are indicated in references. The present study develops, for the first time, the specific role of arterial stiffness and PP, which both have been defined at the early part of this review, and represent 13 publications indicated by PubMed in American Journal of Hypertension. Such observations justify that the present paper has been focused mainly on arterial stiffness and PP.

At this point, it is important to note one of the principal limitations of this study: the difficulty to evaluate in each individual subject the respective contribution of the steady and pulsatile hemodynamic BP components, MAP and PP, in the mechanism of CV risk. This aspect is particularly difficult to evaluate when proteinuria is present. Indeed, important cross-links may be observed between proteinuria, arterial stiffness, and even PP when all these parameters are studied together.

In addition, it is important to note that KDIGO classification of kidney diseases is based not only on GFR category but also on the level of urinary albumin excretion. In such conditions, the respective contribution of MAP and PP to CV risk remains yet difficult to interpret, even in the presence of more adequate evaluations of renal RI. All these aspects are quite important to summarize, when taking into account the 2 main conclusions of this review:

Firstly, in the presence of a significant arterial stiffness gradient (aortic PWV < peripheral PWV), partial
reflections occur distant from microcirculation and return at low PWV to the aorta in diastole, maintaining central to peripheral amplification. It is so important to note that such partial reflections limit the transmission of pulsatile pressure energy to the periphery and thus protects the renal microcirculation.

Secondly, in the disappearance or inversion of stiffness gradient (aortic PWV > peripheral PWV), PP is not sufficiently dampened and thus is significantly transmitted toward the renal microcirculation, contributing to its damage. In parallel, the central to peripheral pressure amplification is attenuated, increasing considerably CV risk. Finally, such conclusions clearly justify the importance to distinguish between MAP and PP in the mechanism of CV risk.

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**DISCLOSURE**

The authors declared no conflict of interest.

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