Role of Pulse Pressure on Cardiovascular Risk in Chronic Kidney Disease Patients

Gema Fernandez-Fresnedo, Emilio Rodrigo, Angel Luis Martin de Francisco, Saturnino Sanz de Castro, Olga Castañeda, and Manuel Arias

Nephrology Service, Universitary Hospital Marqués de Valdecilla, Santander, Spain

Epidemiologic studies have emphasized the close relationship between high BP and cardiovascular disease (CVD). Recently published prospective studies have focus on systolic and pulse pressure (PP). Systolic BP seems to be a more important factor than diastolic BP on cardiovascular and all-cause mortality in older patients. PP reflects stiffness of the large arteries and increases with age. Increasingly, PP is recognized as an independent predictor of myocardial infarction, congestive heart failure, and cardiovascular death, even in hypertensive patients who undergo successful antihypertensive drug therapy, especially in older individuals. Chronic kidney disease (CKD) is a major public health problem. The progression of kidney disease and its associated cardiovascular complications are the major causes of morbidity and mortality. This holds true for all stages of kidney disease, including ESRD that requires renal replacement therapy. Most of the traditional CVD risk factors are highly prevalent in CKD, and several nontraditional factors also are associated with atherosclerosis in CKD. The burden of hypertension is present at all stages of CKD. Several studies have shown that PP is a reliable prognostic factor for mortality and CVD in patients who have CKD and are on hemodialysis and in renal transplant patients. The purpose of this review is to show the importance of PP on cardiovascular risk in patients with CKD, including kidney transplant recipients.


C hronic kidney disease (CKD) is a worldwide public health problem. There is a rising incidence and prevalence of ESRD, with poor outcome and high cost. ESRD that requires treatment with dialysis or transplantation is the most visible outcome of CKD. However, cardiovascular disease (CVD) also frequently is associated with CKD, which is important because individuals with CKD are more likely to die of CVD than to develop ESRD (1). CVD in CKD is treatable and potentially preventable, and CKD seems to be a risk factor for CVD (2). In 1998, the National Kidney Foundation Task Force issued a report that emphasized the high risk for CVD in CKD (3). This report showed that there was a high prevalence of CVD in CKD and that mortality as a result of CVD was 10 to 30 times higher in dialysis patients than in the general population. The task force recommended that patients with CKD be considered in the highest risk group. Go et al. (4) demonstrated that reduced estimated GFR <60 ml/min per 1.73 m² independently predicts the risk for death and cardiovascular events in individuals with or without known CVD.

Most of the traditional CVD risk factors, such as older age, diabetes, systolic hypertension, left ventricular hypertrophy, and low HDL cholesterol, are highly prevalent in CKD. Several nontraditional factors, such as hyperhomocysteinemia, oxidant stress, dyslipidemia, and elevated inflammatory markers, are associated with atherosclerosis. Oxidant stress and inflammation may be the primary mediators or the “missing link” that could explain the tremendous burden of CVD in CKD (2). The purpose of this review is to show the importance of pulse pressure (PP) as clinical marker of cardiovascular risk in patients with CKD.

PP as Cardiovascular Risk Factor

The principal components of BP consist of both a steady component (mean arterial pressure [MAP]) and a pulsatile component (PP). Major determinants of MAP are ventricular ejection and peripheral vascular resistance. PP, the difference between systolic BP (SBP) and diastolic BP (DBP), also is made up of two major components: one that is caused by ventricular ejection’s interacting with the viscoelastic properties of the large arteries (direct) and the other one that is caused by wave reflection (indirect). PP reflects stiffness of the large arteries and increases with advancing age from 50 yr onward, because of opposing trends in SBP and DBP (5). Although a large PP as measured at the brachial artery with the use of the cuff method is not an accurate representation of the proximal aortic PP, it does suggest a stiffened aorta. When the vascular compliance is normal, the reflected waves return during diastole and will augment the diastolic pressure wave (6). Consequently, atherosclerosis simultaneously tends to increase SBP and lower DBP, resulting in a widened PP, which paves the way for CVD morbidity because elevated SBP is associated with a greater left ventricular workload, enhancing myocardial wall stress and oxygen demand. In addition, the decreased DBP may result in a reduced coronary perfusion pressure, resulting in a decreased myocardial oxygen supply and a greater risk for myocardial ischemia and infarction.
From a methodologic viewpoint, the concept that the pulsatile component of BP per se plays a role in CVD morbidity and mortality in addition to (or independent of) SBP, DBP, and MAP is difficult to demonstrate. Indeed, PP is only the mathematical difference between SBP and DBP; therefore, it raises the problem of artifactual interpretations. However, PP increasingly has become recognized as an independent marker for the development of CVD, and several large outcome trials have supported this notion. Franklin et al. (7) from the Framingham Heart Study, Millar et al. (8) from the Medical Research Council trial, and Blacher et al. (9) from the European Working Party on High Blood Pressure in the Elderly Trial (EWPHE), Systolic Hypertension in China Trial (Syst-China), and Systolic Hypertension in Europe Trial (Syst-Eur) trials showed clearly that PP is a stronger cardiovascular risk factor than SBP alone for myocardial infarction in populations of individuals with hypertension. In the meta-analysis of the three trials concerning systolic hypertension in the elderly by Blacher et al., an increase of 10 mmHg in PP increased the risk for all coronary end points by 13% and for cardiovascular mortality by nearly 20%. In the treatment arm of the Systolic Hypertension in the Elderly Program (SHEP) trial but not in the placebo arm, a higher PP was an independent predictor of heart failure and stroke. A 10-mmHg increase in PP was associated with a statistically significant 32% increase in risk for heart failure and a 24% increase in risk for stroke after controlling for SBP and other risk factors. These results suggest that PP is a useful marker of risk for heart failure and stroke among older adults who are treated for isolated systolic hypertension (10).

Controversy exists as to whether it is the PP or the SBP that is the more important prognostic measure of CVD. However, it seems that both bodies of evidence may not be mutually exclusive. In a study that evaluated the risk for cardiovascular mortality as a result of the combined changes in systolic BP, Benetos et al. (11) showed that patients who experienced increased SBP while their DBP decreased had the highest risk for cardiovascular mortality after adjustment for age and other risk factors. The same basic result was found by Staessen et al. (12): At any given level of BP, the risk for death rose with lower DBP and, therefore, with greater PP. This suggests that an increased SBP and decreased DBP are more harmful than other causes of increased PP, such as heightened stroke volume. Furthermore, some studies have indicated clearly that cardiovascular risk is related not only to an increase in SBP but also to a decrease in DBP (9). At any given value of SBP, cardiovascular risk is higher when DBP is lower. In middle-aged and elderly individuals, coronary heart disease (CHD) risk increased with lower DBP at any level of SBP >120 mmHg, suggesting that higher PP was an important component of risk (7).

In a large population of 19,083 normo- and hypertensive men who were followed for 20 yr, Benetos et al. (13) confirmed not only that increased PP was a strong predictor of myocardial infarction but also that this predictive value was observed in the normotensive population, particularly in men who are older than 55 yr. This analysis may be applied even to treated hypertensive individuals. As a result, even within normotensive BP ranges (SBP ≤140 mmHg, DBP ≤90 mmHg) after successful drug therapy, increased PP predicts a reduced cardiovascular mortality rate. This study is the first to show clearly that in a large male unselected population with a relatively low risk, PP measurement may help in the evaluation of the individual risk and therefore in the therapeutic decision making.

Aging plays an important role in influencing the relation of BP indexes to CHD risk. In patients who are younger than 50 yr, DBP is a stronger predictor of CHD risk than SBP or PP, suggesting that increased peripheral resistance and altered peripheral pulse-wave amplification are dominant in determining CHD risk. Between the ages of 50 to 59 yr, all three BP indexes are similarly predictive of CHD risk, suggesting a balance between small-vessel resistance and large-artery stiffness. From age 60 yr on, there is a shift in favor of PP and SBP as predictors of CHD risk, suggesting that large-artery stiffness with early wave reflection are the dominant hemodynamic determinants of risk. Although DBP predominates over SBP in young adults, the greatest burden of CVD occurs in older individuals with isolated systolic hypertension and a wide PP (14).

Finally, Nawrot et al. (15) suggested that PP may improve the Framingham risk prediction among middle-aged and older, seemingly healthy individuals. An increased PP of >70 mmHg was associated with an approximately fivefold greater risk for future cardiovascular events in association with high versus low Framingham risk score.

**PP in CKD**

The pulsatile component of arterial pressure (PP) varies with age. Franklin et al. (5) found that during the fourth and fifth decades, the increase in PP is small and correlated with the rise in MAP. This could be explained by a “downstream” increase in vascular resistance causing an “upstream” increase in transmural pressure, which in turn chronically stretches large central arteries and increases their stiffness. The normal range and the reference values of PP have not been reported previously except those by Asmar et al. (16). These authors showed that 50 mmHg likely was the reference value for PP in 61,724 ambulatory unselected individuals in France. Tozawa et al. (17) reported that at any MAP level, hemodialysis patients had a higher SBP and PP and lower DBP values than control subjects who had normal renal function and were matched for age, gender, diabetes, and body mass index. The PP value in the control group was similar (49 mmHg) to the PP value in the group of Asmar et al. (16). Age and diabetes were significant predictors of elevated PP in both normal subjects and hemodialysis patients. A loss of compliance in large arteries is associated with aging, as described in the previous section, and diabetes accelerates the decrease in compliance of the vessel and stiffening of arteries results in increased PP (17). PP was extremely high in the majority of 37,069 patients who were undergoing hemodialysis and were analyzed by Klassen et al. (18), with fewer than 10% of patients having PP <50 mmHg. Likewise, the 1243 chronic hemodialysis patients who were analyzed by Tozawa et al. (19) had a mean PP of 70.6 ± 18.1 mmHg. In multiple linear regression analysis, age, body mass index, duration of dialysis, serum albumin, antihypertensive treatment, and diabetes were significant predictors of PP (19).
Banerjee et al. (20) analyzed predialysis patients with CKD stages 4/5 and found a mean PP of 66 mmHg. Similarly, 27% of transplant patients from our center had PP values ≥65 mmHg, with a significant correlation with age and presence of diabetes (Figure 1) (21). In conclusion, patients with CKD show higher PP values than control subjects with normal renal function.

**PP and Cardiovascular Risk in ESRD**

The ability of arteries to accommodate instantaneously the volume that is ejected by the left ventricle usually is described in terms of compliance, distensibility, or stiffness of the aorta or an individual artery. The most common method to evaluate arterial stiffness is based on the study of pulse-wave velocity along a given large artery, such as the aorta. Arterial stiffness increases with age, hypertension, diabetes, and ESRD. Blacher et al. (22) showed the first evidence that in patients with ESRD, increased aortic stiffness, determined by measurement of aortic pulse-wave velocity, was a strong independent predictor of all-cause and mainly cardiovascular mortality. The limitation of pulse-wave velocity measurements is their inability to differentiate directly between functional and structural factors that contribute to stiffness. Hence, PP could be used as a crude guide to stiffness.

Several studies have demonstrated the association between PP and an increased death risk in hemodialysis patients. Klassen et al. (18) reported that an incremental increase of 10 mmHg in postdialysis PP was associated with a 12% increase in the hazard for death. The amount of variability in mortality that was accounted for by PP was similar to that seen for race, hematocrit level, years on dialysis, or parathyroid level. PP was significantly associated with mortality only in patients with SBP ≥140 mmHg. When PP increased within each category of SBP, the percentage of patients who died at 1 yr also increased. As SBP increased within each category of PP, the death percentages decreased until pressures reached >165 mmHg, at which point some groups displayed an increase in death (reverse J curve). The interaction between PP and age was significant. The risk that was associated with PP in the younger half of the cohort (age <62 yr) was approximately two times the risk that was associated with PP in the older half (hazard ratio 1.24 versus 1.12) (18). Tozawa et al. (19) analyzed 1243 chronic hemodialysis patients, and the major findings of this 9-yr follow-up study were that baseline PP independently predicted the incidence of total mortality in nondiabetic patients and that the wider the range of PP, the greater the increased risk for mortality. The association with the risk for total mortality was positive for PP and SBP but NS for DBP, considering each pressure individually. When SBP and DBP were entered jointly into the Cox regression model, the association with the risk for total mortality was positive for SBP and negative for DBP. After the addition of diabetes as an adjusted variable to the model, PP was not a significant predictor for total mortality. PP was positively associated with the risk for stroke and acute myocardial infarction. The results of this study not only support the results of previous reports but also confirm that higher SBP and lower DBP values, that is, a wider PP range, correlate with a significant risk for death in patients who are on hemodialysis. Furthermore, in this study, the power of PP to predict total mortality was more potent than that of SBP or DBP alone.

The significance of PP in predialysis patients has not been studied adequately. Banerjee et al. (20) established that elevated PP was associated with increased probability of reaching adverse end points, including death and progression of renal disease that requires dialysis in predialysis patients with CKD stages 4/5. The use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was associated with better event-free survival. It may be possible that inhibition of the renin-angiotensin system renders the central arteries more distensible and, thereby, overcomes the hemodynamic consequences of elevated PP.

In renal transplant recipients, it is known that hypertension is a common complication, with prevalence higher than 50% in patients with well-functioning grafts; it is associated with increased mortality and with worse graft survival (23). CVD now is the major cause of death in renal transplant recipients, especially after the first year after transplantation. We investigated the effect that a wider PP may have on CVD after renal transplantation in 532 transplant patients who were classified into two groups depending on 1-yr PP (< or ≥65 mmHg). A wider PP range that resulted from a higher SBP and lower DBP correlated with a significant risk for cardiovascular complication in transplant patients (21). In a Cox regression model, increased PP was associated with higher CVD (relative risk 1.73; 95% confidence interval 1.13 to 2.32; P < 0.01).

**Conclusion**

Currently, the mechanical factors that predict cardiovascular risk are no longer limited to the two arbitrary and specific points of the BP curve: Peak SBP and end DBP. Other mechanical factors that are derived from the study of pulsatile arterial hemodynamics are emerging as markers of cardiovascular risk. The evidence that a widened PP is an independent marker of
cardiovascular risk is well established. PP is elevated in patients with CKD, and it seems to be a significant predictor of risk for mortality and morbidity. However, the effect of PP reduction on the prognosis for patients with CKD remains to be determined; therefore, more evidence is necessary to consider PP reduction as a therapeutic target in the treatment of patients with CKD.

References