end-stage renal disease with well-controlled secondary hyperparathyroidism, concentrations of these biomarkers reach levels that are 10-fold higher than in nonuremic controls.[9] This is remarkable because, according to recent registry data, low or normal bone turnover is the most common finding in these patients. These data indicate that CTX, NTX, and OC, as opposed to TRAP5B, BSAP, and trimeric P1NP, are at least partly cleared by the kidneys, compromising their use as indicators of bone turnover. In the present study, significant differences between kidney donors and controls were observed mainly for those biomarkers that are cleared by the kidneys. To what extent the higher levels of OC, NTX, and CTX in kidney donors reflect increased bone turnover versus renal retention remains to be determined. One might argue that the higher BSAP and P1NP concentrations in kidney donors at least suggest increased bone formation. However, statistical issues such as imbalances at baseline (BSAP) and the (defendable) strategy not to correct for multiple comparisons also warrant prudent interpretation.

Current evidence indicates that living kidney donation confers great benefit to recipients, whereas the price paid by donors seems limited. It is our obligation to correctly inform and carefully evaluate candidate kidney donors and provide intensive and lifelong monitoring after donor nephrectomy for incident chronic kidney, disturbances of mineral and bone metabolism, and cardiovascular disease. In order to be able to provide optimal counseling, long-term epidemiological studies based on real data rather than projections are mandatory. This also applies to mineral and bone metabolism. In this regard, bone mass and microarchitecture as assessed by imaging techniques might be relevant outcome parameters in addition to bone biomarkers. However, only the evaluation of fracture incidence will provide definitive information. The ALTOLD study illustrates that there is smoke; let us be prepared for fire.

DISCLOSURE

PE has served as a consultant for or received honoraria from Amgen, Sanofi, Tecomedical, and Shire. The other author declared no competing interests.

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Estimating central blood pressure in the extreme vascular phenotype of advanced kidney disease

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Carlsen *et al.* demonstrated that the estimation of central blood pressure from peripheral tonometry does not work properly in patients with chronic kidney disease. We explore here the implications of this finding, first by considering the technical conditions for validating central BP monitors, then by discussing the possible causes for discrepancies between chronic kidney disease patients and usual study populations. Lastly, we review the merits and limits of the work by Carlsen *et al.*

Kidney International (2016) **90,** 736–739; http://dx.doi.org/10.1016/j.kint.2016.06.039

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High blood pressure (BP) is among the key causes of chronic kidney disease (CKD); therefore, accurate BP measurement is critical for correct diagnosis and care. The usual approach to assessing risk related to BP relies on measurements taken by cuff at the upper arm on the assumption that this is a reasonable representation of BP exposure to the target organs, including the kidneys. However, human studies of invasively measured BP have demonstrated this is not necessarily the case, with the possibility for a high degree of variability in systolic BP (SBP)

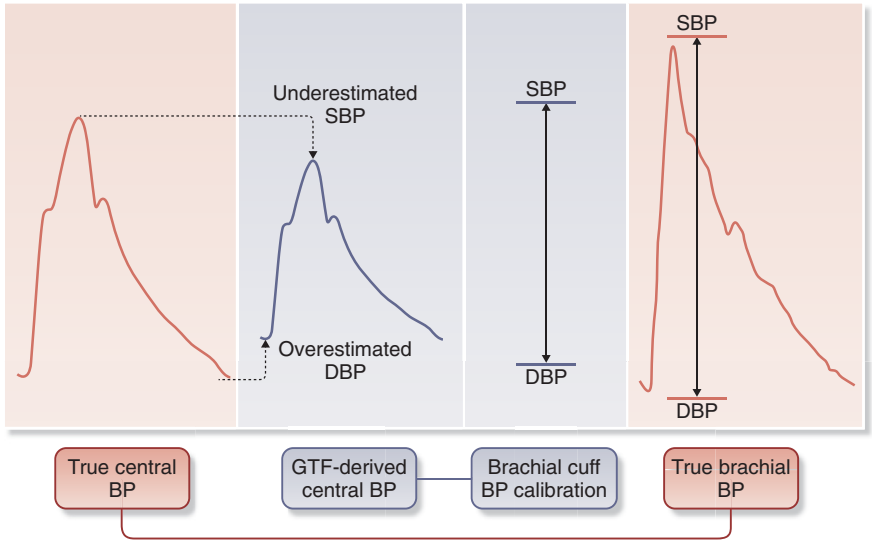

Figure 1 | Example of central and brachial true (invasive) arterial pressure waveforms and the consequent error in generalized transfer function (GTF)-derived central blood pressure (BP) with waveform calibration using brachial cuff BP. DBP, diastolic blood pressure; SBP, systolic blood pressure.

measured within the aorta compared with the peripheral limb arteries.[1,2] This observation alone has potential ramifications for correct hypertension diagnosis based on upper arm BP, but perhaps even more importantly, the SBP response to vasoactive drugs can differ markedly between the aorta and brachial artery.[3] Given that central BP more closely represents the pressure experienced by organs such as the kidneys, there is an expectation for central BP to be more clinically relevant than brachial cuff BP. Indeed, this has been demonstrated with invasively measured central BP,[4] and altogether these data imply that greater precision in hypertension management may be achieved with knowledge of an individual's central BP to help guide care.[5]

Because intra-arterial BP measurement is not feasible for widespread application, techniques have been developed to noninvasively estimate central BP through various methods, including from the application of a generalized transfer function (GTF) to the radial artery BP waveform recorded by applanation tonometry. This method has been widely used in clinical research and has produced sufficient evidence to justify reimbursement for central BP monitoring through the US Centers for Medicare and Medicaid Services. Many performance criteria, including validation, are required to achieve such an endorsement. In this regard, the method has been mostly compared with invasive BP primarily among patients with preserved kidney function undergoing coronary artery angiogram procedures, but seldom in special populations such as children or patients with specific diseases. The work by Carlsen *et al.*[6] (2016) in this issue of *Kidney International* presents essential new information on the performance of central BP estimation by radial applanation tonometry among patients with severity of CKD varying from stage 3 to 5.

The rationale for the study was based on advanced CKD being associated with serious vascular irregularities that may alter the normal BP relationship between the aorta and peripheral arteries and, therefore, potentially affecting the GTF-derived central BP, which may have clinical implications for the utility of central BP. Sequential measures of invasive central aortic BP, brachial oscillometric cuff BP, and GTF-derived central BP were recorded among 41 control participants and 83 patients with CKD referred for elective coronary angiography. The principal goals were to determine the effect of CKD and aortic stiffness on the accuracy of noninvasive central BP, with invasive central BP as the reference standard.

Notable findings were that GTF-derived central SBP had acceptable accuracy when radial pressure waveforms were calibrated using invasive central mean arterial pressure (MAP) and diastolic BP (DBP),[6] which emphasizes the validity of the GTF when correct calibration of radial waveforms is applied, as reported by other investigators. However, of interest was a significant trend for underestimation of central SBP with declining estimated glomerular filtration rate (eGFR), even when using this invasive calibration standard. Furthermore, when radial pressure waveforms were calibrated using the cuff brachial SBP and DBP, as would be the case in clinical practice, there was major underestimation of central SBP. This has been reported previously and is not unexpected because many cuff BP devices will underestimate the true brachial SBP but overestimate true brachial DBP, and thus introduce a calibration error that is then passed on to the (under)estimation of central SBP and pulse pressure (as summarized in Figure 1). On the other hand, a critical new finding was that the degree of central SBP underestimation followed a stepwise association with deteriorating renal function and increasing aortic stiffness. Also, Carlsen *et al.*[6] found that the cuff brachial SBP had closer association with invasive central SBP than with GTF-derived central SBP estimates, and they concluded that hypertension management may be more reliable when based on standard brachial cuff BP.

The implications of the Carlsen *et al.*[6] findings are that pathophysiological factors related to advanced renal disease may induce error in GTF estimation of central SBP when using radial applanation tonometry in clinical practice, and this could result in underappreciation of the true level of risk related to BP among these patients. But what could explain these findings? A possible clue may come from the observation that GTF-derived central SBP was progressively underestimated as renal disease worsened even when invasive aortic MAP and DBP were used