Polar Views in Nephrology

Pro: Ambulatory blood pressure should be used in all patients on hemodialysis

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ABSTRACT

In the adult population in general and among people with chronic kidney disease in particular, it is now well established that hypertension is a major driver of renal disease progression and cardiovascular morbidity and mortality [1–4]. Although the contribution of hypertension to cardiovascular morbidity and mortality among patients on long-term dialysis continues to be debated [5–8], a major barrier to detect hypertension as a risk factor for cardiovascular events in these patients has been the inability to diagnose hypertension [9]. Largely to blame has been the easy availability of pre-dialysis and post-dialysis blood pressure recordings in stark contrast to ambulatory blood pressure measurements in dialysis patients to accurately diagnose the presence or control of hypertension [10]. It is increasingly becoming clear that out-of-office blood pressure recordings are superior to clinic recordings in making a diagnosis, assessing target organ damage, evaluating prognosis and managing patients with hypertension [11–15]. In this debate, I have been asked to defend the position that ambulatory blood pressure recordings should be systematically applied to all patients on hemodialysis.

Keywords: ambulatory blood pressure monitoring, diagnosis, hemodialysis, hypertension, mortality

INADEQUACY OF PRE- AND POST-DIALYSIS BLOOD PRESSURE RECORDINGS TO DIAGNOSE HYPERTENSION

Among patients on hemodialysis, dialysis unit recordings of blood pressures are insufficient for making a diagnosis of hypertension [10]. Although blood pressure declines in the majority of the patients from pre-dialysis to postdialysis in a predictable way, the magnitude of the change and sometimes the directionality of this change can be variable among patients and often within the same patient from one visit to the next [16]. If variability were the sole factor that impairs the diagnosis of hypertension, one may speculate that averaging a large number of readings might yield a better baseline and therefore assist in the diagnosis of hypertension. However, among hemodialysis patients on long-term dialysis, even 2-week averages of pre-dialysis or post-dialysis blood pressure recordings are unable to accurately determine the presence or absence of hypertension [17]. Volume expansion and accumulation of uremic factors are probably in large part responsible for the poor ability of blood pressures obtained within the dialysis unit to predict hypertension in the interdialytic period [18]. Poor technique of blood pressure measurement has often been blamed to be the cause of the poor performance of pre- or post-dialysis blood pressures to diagnose hypertension in such patients [19]. However even when great attention is paid to the technique of blood pressure measurements, pre- and post-dialysis blood pressure recordings even when averaged over 2 weeks are insufficient for making a diagnosis of hypertension [20].

HOME BLOOD PRESSURE RECORDINGS

If pre- and post-dialysis blood pressure recordings are insufficient, the next question to pose is whether blood pressures obtained by the patients can make a better diagnosis. In a prospective diagnostic test study, 150 patients on long-term chronic hemodialysis had measurements of both pre- and post-dialysis blood pressures and home blood pressure recordings [20]. Home blood pressures were obtained three times daily for 1 week using an automatic oscillometric monitor by the...
patients. These recordings were compared to the interdialytic ambulatory blood pressure recordings obtained over 44 h between two dialysis treatments. The area under the receiver operating characteristic curve of home blood pressure was 0.89. This means that if home blood pressure recordings were used to make a diagnosis of hypertension it would be correct 89% of the time. In other words, home blood pressures were able to diagnose hypertension with an accuracy of 89%. An average home blood pressure ≥150 mmHg had a sensitivity of 80% and specificity of 84.1% in making a diagnosis of hypertension with the gold standard method of interdialytic ambulatory blood pressure monitoring [20]. Home blood pressures were similar to ambulatory blood pressures when predicting target organ damage such as left ventricular hypertrophy [21]. Furthermore two separate studies have demonstrated that home blood pressure recordings are associated with prognosis [22, 23]. The first was a prospective cohort study of 150 chronic hemodialysis patients who underwent blood pressure measurements using four methods: home blood pressure three times daily for 1 week, over an interdialytic interval by ambulatory recording, and by ‘routine’ and standardized methods in the dialysis unit over 2 weeks [22]. Patients were followed for a median of 24 months to assess the end points of all-cause and cardiovascular mortality. Cardiovascular death occurred in 26 (17%) patients and death in 46 (31%) patients. A 1-SD increase in systolic BP increased the risk for death by 1.35 (95% CI 0.99 to 1.84) and in diastolic BP by 1.40 (95% CI 1.03 to 1.93) for home BP and between 0.97 and 1.19 (P > 0.20) for all-cause mortality for dialysis unit BP recording. In comparison, in the case of ambulatory BP recording, 1-SD increase in systolic BP increased the risk for death by 1.46 (95% CI 1.09 to 1.94) and in diastolic BP by 1.47 (95% CI 1.09 to 1.99). In a second study of an expanded cohort, 326 patients on dialysis were followed over a median of 32 months after measurements of dialysis unit, home, and ambulatory recordings [23]. Over a mean follow-up of 32 (SD 20) months, 102 patients died (31%), yielding a crude mortality rate of 118/1000 patient years. Systolic but not diastolic blood pressure was found to be of prognostic importance. Adjusted and unadjusted multivariate analyses showed increasing quartiles of ambulatory and home systolic blood pressure to be associated with all-cause mortality (adjusted hazard ratios for increasing quartiles of ambulatory: 2.51, 3.43, 2.62; and for home blood pressure: 2.15, 1.7, 1.44). Mortality was lowest when home systolic blood pressure was between 120 and 130 mm Hg and ambulatory systolic blood pressure was between 110 and 120 mmHg. Blood pressure recorded before and after dialysis was not statistically significant (P = 0.17 for pre-dialysis, and P = 0.997 for post-dialysis) in predicting mortality. Out-of-dialysis unit blood pressure measurement provided superior prognostic information compared to blood pressure within the dialysis unit (likelihood ratio test, P < 0.05).

Studies have also revealed that home blood pressure-guided therapy to manage hypertension among hemodialysis patients is superior to pre-dialysis blood pressure-guided therapy in...
controlling hypertension [24]. In a randomized controlled trial, compared to pre-dialysis blood pressure recordings, better control of ambulatory blood pressures was obtained at 6 months when patients were treated using home blood pressure-guided therapy [24]. Furthermore, in a recent randomized trial, hypertension in hemodialysis patients treated with atenolol or lisinopril (HDPAL), home blood pressure recordings were used to manage hypertension over the course of 1 year [25]. An abbreviated scheme of home blood pressure monitoring was used in such patients. Patients measured blood pressures on waking and before going to bed, that is twice daily for 4 days after the midweek dialysis. An average of these blood pressures was sufficient to manage hypertension over the long-term in the research setting.

**AMBULATORY BLOOD PRESSURE RECORDINGS**

The next question that then emerges is whether ambulatory blood pressure monitoring is superior to home blood pressure monitoring. Interdialytic ambulatory blood pressure monitoring is held to be the gold standard for the diagnosis of hypertension [26]. Of course a greater number of readings can provide a better average. However, even if a few blood pressure recordings were randomly taken from the entire 44 h recordings it compares better with the dialysis unit recordings when associated with the outcome of all-cause mortality [27]. Thus the location of measurement matters; making a diagnosis of hypertension using even a few measurements of ambulatory recordings is superior to recordings made in the dialysis unit [27]. This concept was further tested in a prospective multicenter study; the Chronic Renal Insufficiency Cohort recently reported the all-cause mortality outcomes related to dialysis unit and out-of-dialysis unit measurements among 326 participants [28]. As seen in other dialysis cohorts [29, 30], a U-shaped association emerged between dialysis-unit systolic blood pressure and mortality [28]. In contrast, there was a linear association between out-of-dialysis-unit systolic blood pressure and mortality [hazard ratio, 1.26 (95% confidence interval, 1.14–1.40) per every 10 mmHg increase].

Ambulatory blood pressure monitoring also has the strongest relationship of any blood pressures with mortality and are discussed above [22, 23]. Ambulatory blood pressure recordings and home blood pressure recordings cannot be used interchangeably. Ambulatory blood pressures tend to be lower than those self-obtained by the patients at home. In a study comparing

**FIGURE 2:** Patterns of systolic and diastolic BP obtained using ambulatory BP monitoring over 44 h during an interdialytic period and analyzed using the trended cosinor change model. The solid line is the control group and dashed line the ultrafiltration (UF) group. The left panel represent recordings at baseline, the center panel measurements at 4 weeks and the right panel 8 weeks following randomization. UF caused a reduction in intercept systolic and diastolic BP but steepened the slope of change over time at 4 and 8 weeks. The amplitude of variation increased in the control group compared to UF group at 4 and 8 weeks in the case of diastolic but not systolic BP. Reproduced from Agarwal R, Hypertension 2009; 54: 241–247.
home BP to ambulatory BP recordings, the blood pressure recording associated with a lower mortality was different for the two measurements. In the case of home BP, a systolic BP between 125 and 145 mmHg and in the case of ambulatory BP, a systolic BP between 115 and 125 mmHg was associated with the lowest mortality [22]. Another advantage of ambulatory blood pressure is that recordings can be obtained during sleep. Data suggest that the blood pressure during sleep and the change from a wake to sleep can be of prognostic importance [31–34]. However, recordings can also be made during periods of activity. In contrast, home blood pressure recordings can only be obtained while the patient is seated and resting. Unlike home blood pressure recordings that can be susceptible to increases during the measurement because of anxiety, ambulatory blood pressures are less likely to be disturbed. A recent meta-analysis suggests that home blood pressures cannot be an adequate proxy of ambulatory blood pressures [35].

Two other dimensions of ambulatory blood pressure recordings have not received much attention, and I will emphasize them here: the recognition of blood pressure patterns [36] and the discovery of a volume signature [37]. Invasive blood pressure recordings or more practical ambulatory blood pressure recordings are the only ways to make possible the recognition of patterns of blood pressure over the interdialytic interval. Blood pressure rises in a predictable manner in the interdialytic period. Usually it is lowest just following dialysis and highest just before dialysis. Blood pressure varies depending on activity levels [38]; activity level and therefore blood pressure demonstrates circadian variation due to sleep and wake cycle [39]. In people not on dialysis, the variation of blood pressure is around a steady mean; thus, circadian variation can be described mathematically by a cosinor model [40]. In contrast, in dialysis patients, there is a steady rise in blood pressure in the interdialytic period in part due to interdialytic weight gain [41]. Accordingly, the trended cosinor model better describes the pattern of blood pressure in the interdialytic period (Figure 1) [36]. Using this model, it was evident in a sample of 136 hemodialysis patients that a greater number of

![Graph](image_url)

**FIGURE 3:** Mean changes in intercept, slope and amplitude over 44 h during an interdialytic period and analyzed using the trended cosinor change model. Solid bars show the change from baseline in the control group and hatched bars the change from baseline in the ultrafiltration (UF) group. Stars indicate $P < 0.05$ for the difference between changes from baseline. Means are maximal likelihood estimates from the statistical model described in the text. The error bars represent the 95% confidence interval of the mean and when they cross zero, the mean change is not distinguishable from zero. Compared to the control group, intercept systolic BP fell 10 mmHg from baseline at 4 weeks ($P < 0.0001$) and 8.1 mmHg from baseline at 8 weeks ($P < 0.0001$) in the UF group. Compared to the control group, slopes of systolic BP steepened by 0.192 mmHg/h more at 4 weeks ($P < 0.0001$) and 0.141 mmHg/h more at 8 weeks ($P < 0.0001$) in the UF group. There was a greater variation in the amplitude of systolic BP at 4 weeks in both control and UF groups, but no differences between groups at 4 or 8 weeks. Diastolic BP fell 4.8 mmHg more in the UF group compared to control group at 4 weeks ($P < 0.0001$) and 4.9 mmHg more at 8 weeks ($P < 0.0001$) in the UF group. There was a greater variation in the amplitude of systolic BP at 4 weeks in both control and UF groups, but no differences between groups at 4 or 8 weeks. Diastolic BP fell 4.8 mmHg more in the UF group compared to control group at 4 weeks ($P < 0.0001$) and 4.9 mmHg more at 8 weeks ($P < 0.0001$). Slopes of diastolic BP steepened by 0.097 mmHg/h more at 4 weeks ($P < 0.0001$) and 0.100 mmHg/h more at 8 weeks ($P < 0.0001$) in the UF group compared to the control group. The amplitude of diastolic BP variation increased in the control group by 1.2 mmHg ($P = 0.01$) more compared to the UF group at 4 weeks. At 8 weeks a fall in the amplitude of diastolic BP variation in UF group lead to a difference of $−2.7$ mmHg ($P < 0.0001$) compared to controls. Reproduced from Agarwal R, Hypertension 2009; 54: 241–247.
antihypertensive medications was not only associated with greater average but also a flatter slope [36]. This generated the hypothesis whether patients with flatter slopes are volume overloaded. So this concept was tested using interdialytic ambulatory blood pressure recordings in the Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial [42]. In this randomized trial lasting 8 weeks, 100 patients were randomized to reduction in dry-weight by clinical judgment and 50 patients to time controls. Interdialytic 44-h ambulatory blood pressure was obtained in all participants at baseline, 4 weeks and 8 weeks. All patients were hypertensive when assessed by ambulatory blood pressure at baseline. In those assigned to the intervention group, there was both a reduction in average blood pressure and steepening of the slope with dry-weight reduction (Figures 2 and 3) [37]. No such changes were observed in the control group. Thus, ‘volume-overload BP pattern’ on ambulatory BP monitoring is characterized by an elevated intercept and blunted slope pattern [37].

AMBULATORY VERSUS HOME BLOOD PRESSURE RECORDINGS

There are some drawbacks to ambulatory blood pressure monitoring. First of all, the equipment is cumbersome and expensive and the acceptability rate for wearing the blood pressure monitoring for prolonged periods is low. It is difficult to perform repeated ambulatory blood pressure monitoring for the management of patients with hypertension. Whereas ambulatory blood pressure can provide intense sampling over a short period of time such as 24 to 48 h tracking, over a longer period of time such as weeks or months is not feasible. Home blood pressure monitoring, on the other hand, because of its infrequent and unobtrusive nature, can provide blood pressure data dispersed over weeks, months, or years. Ambulatory blood pressure monitoring can disrupt sleep. If sleep is disrupted the dipping status would be difficult to ascertain as has been demonstrated in prior studies [43].

CONCLUSIONS

In summary, ambulatory blood pressure monitoring is the gold standard of blood pressure measurement. Without ambulatory blood pressure monitoring it is difficult to be certain if the patient is hypertensive or normotensive. Accordingly, I conclude that ambulatory blood pressure monitoring should be systematically applied among all dialysis patients. Although ambulatory blood pressure monitoring is the gold standard for making a diagnosis of hypertension in hemodialysis patients, I concede that home blood pressure monitoring is a practical way to manage these patients over the longterm.

ACKNOWLEDGEMENTS

This work was supported by the National Institutes of Health (grants 2R01-DK063020-10).

CONFLICT OF INTEREST STATEMENT

None declared.


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Opponent’s comments

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Dr Agarwal presents a passionate argument for the use of ambulatory blood pressure monitoring (ABPM), but fails to address the added value of this measurement, or the practical use of ABPM beyond research studies and trials. ABPM provides more information on BP than home monitoring, single clinic readings or even the ‘before and after’ readings that we routinely collect on dialysis. The additional detail that ABPM and, to a lesser extent, home readings provide clearer associations between blood pressure parameters and outcomes in the dialysis population. This reflects the repeated measurements and is a strength of ABPM in epidemiological studies and clinical trials [1]. However, it does not necessarily help in the management of individual patients. Dr Agarwal argues that the pattern of change in interdialytic BP demonstrated by ABPM identifies patients with large fluid gains. While I—and I suspect everyone else—would agree that this is a major problem, with proven links to adverse outcomes [2], I suspect that no one would advocate the use of ABPM to direct fluid management—preferring anything from weight and clinical assessment to lung ultrasound and echocardiography.

One of the issues about focusing on a single technique or measurement is that it detracts from the bigger picture. Dr Agarwal argues that failure of the AURORA trial to identify