Commentary

The internist’s role in treating hypertension in hemodialysis patients

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Summary

Hypertension in hemodialysis patients is typically treated with a combination of volume removal with dialysis—although limited by current dialysis paradigms—and hypertension medications. Unfortunately, most patients treated in this manner remain hypertensive. This contrasts with superior results obtained in clinical studies in which salt restriction and augmented dialytic volume removal normalized blood pressure without requiring medicines. These results are consistent with the role of excess volume as the main etiology of hypertension in end-stage renal disease (ESRD). Interdialytic blood pressure is now recognized as important to patient prognosis. These measurements are frequently obtained by internists at office visits. Internists and nephrologists should address both peri-dialysis and interdialysis hypertension in a collaborative manner. This strategy should focus on, as much as reasonably possible, salt restriction and dialytic volume removal rather than hypertension medicines.

Introduction: interdialytic hypertension

Most patients with end-stage renal disease (ESRD) treated with hemodialysis remain hypertensive by the usual criteria1–3—75% of 69,590 patients in a national dialysis chain had a predialysis systolic blood pressure >140 mmHg.2 Unfortunately, the optimal blood pressure for hemodialysis patients has not been established by randomized, controlled trials. Observational studies demonstrate, surprisingly, that predialysis systolic blood pressure is not associated with increased mortality until it reaches as high as 190 or 200 mmHg.1,2 Predialysis systolic blood pressures in the ‘normal’ range—140 mmHg or less—are actually associated with increased mortality in ESRD.1,2,4

These studies, however, suffer the usual limitations of observational methodology and do not demonstrate that lowering predialysis blood pressure is harmful. In addition, due to volume fluxes with dialysis and in the interdialytic period, blood pressure in hemodialysis patients varies, allowing for the possibility that all measurements are not equally important. Although national guidelines5 focus on dialysis-associated measurements, it is not a priori apparent that values obtained during these few, discrete, short-time periods (~12 h out of the week) will accurately represent a patient’s typical blood pressure or relate to prognosis. In fact, in contrast to the results obtained looking at pre- and postdialysis measurements, Alborzi et al. found that lower systolic blood pressures—125 to 145 mmHg—in the interdialytic period were associated with the best outcomes.6 This prospective cohort study, following 150 patients for 2 years, also found that interdialytic measurements were more closely related to prognosis than dialysis-associated values.6

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Although some patients monitor their own blood pressure and may have access to ambulatory monitoring, many interdialytic measurements are obtained, or may most easily be obtained, by internists during office visits. Given the evidence that these measurements are more important than peri-dialysis values, the internist’s approach to interdialytic hypertension should be examined. This article will address the necessary collaboration between internists and nephrologists treating hypertension in hemodialysis patients at different points in the dialysis and interdialysis cycle.

**Controlling hypertension without medicines**

A review of successful hypertension strategies previously reported in hemodialysis patients reveals an interesting discrepancy: Current community practice does not incorporate the approach that has yielded superior results. Whereas successful reports addressed the core hypertension problem of excess volume in ESRD with more aggressive dialytic volume removal (and trivial or no use of medications), current community practice relies much more heavily on hypertension medication. For example, a recent audit of more than 10,000 hemodialysis patients indicated that 91% were prescribed hypertension medicines.7 Perhaps the first step toward improving blood control in hemodialysis patients is to reemphasize that hypertension medicines do not rectify the underlying problem of excess volume, a failure that diminishes their effectiveness.

Although hypertension in hemodialysis patients is multifaceted, it has long been recognized that the main etiology is excess volume (reviewed in8). An important early report by Vertes et al. in 1969 described the successful resolution of hypertension in 35 of 40 ESRD patients treated with volume removal and without any medicines.9 The gradual removal of ~16 pounds of excess volume per patient improved the mean blood pressure from 180/110 to 140/86 mmHg.9 Similar results were later described with more modern dialysis technology, using different techniques to facilitate volume removal, including more frequent,10–12 longer1,13–15 and extra dialysis treatments.15 All were effective and obviated the need for any hypertension medications for most patients.

Fagugli and colleagues used bio-impedance to quantitate volume removal and its effect on blood pressure.10,11 In a prospective two-period crossover study, daily short dialysis decreased extracellular water by 5.1% compared to standard thrice-weekly hemodialysis. This was accompanied by a 20 mmHg decrease in ambulatory systolic blood pressure to 128 mmHg, even as hypertension medicines were discontinued in seven out of eight patients.10 Similarly, 4.5–5 h ‘extended’ thrice-weekly hemodialysis treatments reduced extracellular water 4.6%. Twenty-four hour ambulatory systolic blood pressure decreased 20 mmHg, to a mean value of 137 mmHg, allowing discontinuation of hypertension medicines in 8 of 10 patients.11

The results obtained in Tassin, France are especially important.13,14 With thrice-weekly 8 h per session dialysis treatments facilitating volume removal, hypertension resolved in all patients, without requiring medicines. Remarkably, the 10-year survival was 85%.13 While it is too simple to ascribe this outcome to improved volume removal alone—longer treatments likely have other beneficial effects as well—these results indicate that blood pressure control and long-term survival can be achieved without hypertension medicines.

These studies, using several different strategies for volume removal, are particularly impressive in combination—it seems that in whatever manner one achieves effective volume removal, hypertension typically resolves, with a beneficial effect on left ventricular hypertrophy10–12 and possibly patient survival.13–15

**The potential problems of hypertension medicines in ESRD**

If hypertension can be controlled without medicines, then the provision of these medicines provides unnecessary costs and exposure to potential side effects. Hypertension medications may be particularly problematic in hemodialysis because they may hinder dialytic volume removal and may predispose patients to dialysis-associated hypotension.16–18 Specific pharmacologic characteristics may contribute: for β-blockers, reducing compensatory sympathetic activity; for vasodilators, hindrance of the compensatory vasoconstrictor that helps prevent dialytic-associated hypotension.17 Dialysis-related hypotension is problematic not only because of the morbidity involved with these episodes, but because they may be associated with increased mortality during follow-up.19 Although the link between hypertension medicines and dialysis-associated hypotension has not been established via prospective studies, Ozhaya et al.15 discontinued all hypertensive medicines at study onset and the Tassin clinicians considered it ‘…absolutely essential that all antihypertensive medications be tapered down and stopped’20 in order to maximize volume removal and blood pressure control.
Because of the commonly perceived relationship between hypertension medicines and dialysis-associated hypotension, physicians often withhold the medicines before dialysis, although this can, at times, result in severe predialysis hypertension. Hypertension medicines may, alternatively, be given only after dialysis. This approach, however, has not received extensive evaluation and is also potentially problematic. Prescribing medicines after dialysis at the time when a patient’s blood pressure is typically at its lowest could make some patients prone to postdialysis hypotension.

**A special role for salt?**

Recent evidence suggests that excess salt may have a pathologic effect beyond its role in osmolarity, volume and hypertension. An osmotically inactive sodium pool apparently resides in extracellular matrices and may result in vascular inflammation, myocardial fibrosis and/or hypertrophy, independent of blood pressure. These putative effects are consistent with results of the Trial of Hypertension Prevention. In this study, patients treated with sodium restriction had a 25% reduction in cardiovascular events and a 20% lower mortality than controls, over a 10 year follow-up, even though the systolic blood pressure declined only 1.2 mmHg. Thus, the long-term benefit of salt restriction appeared far greater than what could be attributed to lower blood pressure.

These data imply that even if pharmacologic therapy of hypertension in ESRD was successful, the outcome might be inferior to equivalent blood pressure control achieved with more salt removal with dialysis, as negative salt balance is needed to deplete the pro-inflammatory salt stores. This intriguing possibility was recently evaluated. A cohort of patients treated with aggressive salt restriction and volume control was compared with a cohort that received less volume control and more hypertension medicine adjusted to achieve the same blood pressure (126/75 mmHg). Serial echocardiography demonstrated that accentuation of salt restriction and volume removal for a 1-year period resulted in a lower left ventricular mass index and higher ejection fraction than in the more pharmacologically treated group. This result is consistent with experimental and clinical data and provides another reason for aggressive volume/salt removal and caution with the use of hypertension medicines in ESRD.

Improving sodium balance—whether intended for classic osmotic and volume pathophysiology, to deplete osmotically inactive sodium stores, or both—is difficult when salt intake is significant and large interdialytic volume gains require relatively rapid removal rates that make patients prone to hypotension with dialysis. When hypotension develops, volume removal must cease and the patient remains with excess salt and volume—hypertension then returns. For these reasons, Shaldon and Vienken and Sanders have recently called for a reemphasis on a salt-restricted diet for ESRD patients. Dietary salt restriction will improve sodium balance both per se and by reducing the required rate of salt and volume removal. The latter will reduce the propensity for hypotension during dialysis, with beneficial implications for both blood pressure control and mortality.

**What’s an internist to do?**

Internists typically examine hemodialysis patients on interdialytic days. When these patients present with hypertension, the physician is placed in a difficult situation. Should he provide additional medication—notwithstanding the observed failure rate of pharmacologic treatment and the potential problems of dialysis-associated hypotension? Can we expect him to allow a hypertensive patient to leave the office without additional medication?

Any advice must be couched in terms that respect the absence of randomized, controlled trials and the resulting ambiguities. Nevertheless, while acknowledging these shortcomings, we can still propose an approach that is consistent with the evidence we do have: the common failure of medication, the etiologic role of excess salt and volume and the reported success of salt restriction and augmented dialytic volume removal in reducing blood pressure and left ventricular mass. If, at an office visit, the patient’s systolic blood pressure is elevated but less than a value up to ~190 mmHg (based on the large observational studies), the patient may be sent home without additional hypertension medication. However, reinforcement of salt restriction falls easily within an internist’s purview and is critical. In addition, the patient’s nephrologist or dialysis nursing staff should be informed of the measurement and the need for augmented volume removal with dialysis. If the blood pressure is above ~190 mmHg, then hypertension medication might be justified with a goal of discontinuing the medicine when salt restriction and volume removal are more successful.

The choice of 190 mmHg as a guide to decision-making is somewhat arbitrary and a physician may adjust this value per his own discretion and comfort. This ambiguity does not, however, diminish the
point that a physician should not feel obliged to
treat all interdialytic hypertension with additional
medication.

Although one is not obliged to provide more med-
icine, a physician should not be satisfied with an
elevated blood pressure. To the contrary, interdialytic
hypertension should trigger nonpharmacologic
responses designed to reduce subsequent measure-
ments, including those obtained in the interdialytic
period. The strategy includes both reinforcement of
salt restriction and augmentation of volume removal
with dialysis. Importantly, when this strategy nor-
malized predialysis systolic blood pressure, the
result carried over to the interdialytic period—in
fact, on a background of salt restriction, the Tassin
investigators adjusted dialytic volume removal until
blood pressure was normal during the entire inter-
dialytic period. This finding was recently corrobo-
rated by Agarwal et al.29 in a preliminary report of a
randomized, controlled trial in which augmented
dialytic volume removal resulted in improved inter-
dialytic ambulatory blood pressure.

Therefore, when an internist reinforces dietary salt
restriction and communicates an elevated interdia-
lytic blood pressure measurement to a nephrologist,
and the nephrologist responds by increasing dialytic
volume removal, the physicians are acting in sync to
address the problem throughout the entire cycle.
The success of this coordinated approach should
be assessed not only at dialysis but also at subse-
quent office exams, with particular emphasis on nor-
malizing interdialytic measurements.

What’s a nephrologist to do?

Increasing volume removal with dialysis is, admit-
tedly, a difficult task, particularly within the structure
of thrice-weekly dialysis. As noted, attempted
removal of the volume gained since the previous
dialysis treatment, particularly when large, can result in dialysis-associated hypotension.16–18 The
failures of volume removal to control blood pressure
accounts for the prescription of hypertension
medicines to 91% of hemodialysis patients.7
Unfortunately, that also fails, as 75% of patients
remain hypertensive.2

However, the clinical studies discussed demon-
strated that physicians do not need to accept the
failures of the status quo: modifying the thrice
weekly, sometimes too-short dialysis framework to
augment volume removal can effectively treat
hypertension.10–15 To be sure, the 8 h dialysis ses-
sions provided in Tassin, France and the daily dia-
lysis provided by others may not be broadly feasible
at this time. However, Ozkhaya et al.15 achieved
similar success in treating hypertension via modest
modifications that could be instituted in virtually
any dialysis center. These included the discontinue-
tion of antihypertensive medicines, repetitive accen-
tuation of salt restriction, moderately increased
treatment times (mostly 4 h, occasionally 5 h), occa-
sional extra treatments and patience. With this
accessible approach they achieved a mean predia-
lysis systolic pressure of 121 mmHg in 218 patients
followed for a mean of 47 months, and only nine
patients required a hypertension medicine.15

Patience is required, as gradual (but persistent)
reductions of excess volume—as little as 0.5–1 kg
a week for many weeks—may be needed to make
progress without suffering dialysis-associated
hypotension. Moreover, a ‘lag phenomenon’—a
temporal delay in the response of hypertension to
volume removal—has been documented.8 Volume
excess appears to result in circulating pressor factors
that may persist for several weeks after volume con-
trol has been established.8

The long-term benefits of longer, daily, or extra
treatments have not been verified by randomized
trolled trials. Nevertheless, the evidence sup-
porting longer treatments for multiple aspects of dia-
lysis therapy is considerable.30 In addition to
improved blood pressure control, longer dialysis
allows slower volume removal rates that are asso-
ciated with less intradialytic hypotension31,32 and
importantly, decreased mortality.19,31 While the cur-
rent state of evidence does not demand longer or
more frequent treatments for all patients, these are
viable options for any patient whose blood pressure
control is deemed unacceptable. The current 75%
failure rate with hypertension control2 suggests the
need to reevaluate the notion of the adequate dia-
lysis dose. The current practice is to prescribe the
shortest time needed to achieve standards for toxin
removal. This might be redefined to adjusting the
duration and frequency of dialysis until blood pres-
sure, including during the interdialytic period, nor-
malizes without excessive incidence of intradialytic
hypotension.

When hypertension medicines
are required

In addition to the interim therapy of the severely
hypertensive patient, hypertension medicines may
be indicated if a good-faith attempt at lowering
blood pressure with salt restriction and volume
removal fails. In particular, when salt intake and
interdialytic weight gains are consistently large, or when the dialysis unit cannot provide longer or extra treatments, patients may remain hypertensive. Physicians should respect the reality of this failure and may then supplement the salt restriction and volume removal strategy with medication.

No specific hypertension medicine has been proven clearly preferable for hemodialysis patients. Given that cardiovascular diseases (sometimes clinically silent) are common in ESRD and that angiotensin converting-enzyme inhibitors and β-blockers are effective therapies for these diseases in the general population, it is tempting to extrapolate these successes to ESRD. However, angiotensin converting-enzyme inhibitors provided broadly in ESRD did not significantly reduce mortality in one trial. In two other trials, angiotensin 2 type 1 receptor blockers reduced cardiovascular events, but these were relatively small trials with short follow-up and had inconsistent effects on mortality. No prospective trial of β-blockers broadly prescribed, or specifically for hypertension, has been conducted in ESRD, although retrospective evaluation of the United States Renal Data System suggested a generalized benefit. Preference for renin–angiotensin system inhibitors and/or β-blockers in ESRD is reasonable (and is apparent, based on recent drug audits), but will not be compelling until research establishes a clear benefit in reducing cardiovascular disease in this cohort.

As noted earlier, the perceived relationship between blood pressure medicines and hypotension during or after dialysis has led physicians to variably suggest that medicine (when medicine is needed) be taken before dialysis, after dialysis, or not at all on days of dialysis. These options need to be evaluated by prospective study. It is likely, as a result of patient variations, that the timing of medication should be individualized, rather than follow a single, rigid rule. For example, patients who would otherwise have severe predialysis hypertension might take antihypertensive medicine even on mornings of dialysis, particularly if they are not prone to hypotension during dialysis. On the other hand, patients prone to hypotension during dialysis might take medications only on interdialysis days, to address interdialytic hypertension. Effective individualized therapy will require close collaboration of internists and nephrologists to adjust the choice and timing of antihypertension medicines according to the patient’s own profile. Internists will provide the interdialytic measurements and nephrologists will provide the peri-dialysis measurements and the propensity to hypotension. Thus, collaboration, with integration of the interdialytic values to the dialysis-related blood pressure profile, is necessary for the salt restriction/volume removal strategy, and when supplemental medicines are needed.

Summary

Treatment of hypertension in hemodialysis patients is complicated by the absence of prospective studies that define a clear blood pressure goal and assess specific strategies. Blood pressure variations introduced by volume fluxes, the importance of salt and volume excess and the problem of dialysis-associated hypotension all distinguish hypertension in the hemodialysis patient from that in other patients, and makes effective therapy especially difficult.

The current approach to hypertension in hemodialysis patients—relatively limited volume removal supplemented by medicines—commonly fails, as most patients remain hypertensive with a high incidence of cardiovascular events and an unacceptable mortality rate. In contrast, a number of investigators have demonstrated much greater success in treating hypertension in hemodialysis patients via salt restriction and various means of modifying dialysis to increase volume removal. When this is accomplished, hypertension medications have typically not been required to improve blood pressure; in fact, they have often been discontinued as part of treatment protocols. These successes in lowering blood pressure with salt restriction and volume removal are consistent with the known pathophysiologic role of excess volume in ESRD. Importantly, evidence (admittedly too-limited) suggests that successful volume removal is associated with excellent outcomes. The potential for improved outcomes with augmented volume removal and improved sodium balance is also consistent with developing evidence that sodium has injurious pro-inflammatory effects distinct from its osmotic and pressor effects.

For these reasons, while we await further studies, an argument can be made that nephrologists and internists should coordinate their efforts to treat hypertension in hemodialysis patients by accentuating, as much as reasonably possible, dietary salt restriction and dialytic volume removal rather than hypertension medications. Internists should reinforce salt restriction and communicate interdialytic blood pressure measurements to nephrologists, and nephrologists should attempt to augment dialytic volume removal aiming to improve interdialytic
blood pressure as well as dialysis-associated blood pressure.

References

