Published in final edited form as:

Curr Opin Nephrol Hypertens. 2012 January ; 21(1): 15–23. doi:10.1097/MNH.0b013e32834db3e4.

Interdialytic Ambulatory Blood Pressure in Patients with Intradialytic Hypertension

Peter N Van Buren, Robert Toto, and Julia K Inrig

The University of Texas Southwestern Medical Center-Dallas, Department of Internal Medicine, Division of Nephrology, Dallas, TX

Abstract

Purpose of review—Hypertension is common in hemodialysis patients and contributes to this population's high risk for cardiovascular morbidity and mortality. Patients with intradialytic hypertension, or increases in blood pressure during hemodialysis, have been shown to have the highest risk for these outcomes. The purpose of this review is to describe new findings that shed light on the epidemiology and pathophysiology of intradialytic hypertension and discuss how a better understanding of these mechanisms may lead to improved blood pressure management and outcomes in hemodialysis patients.

Recent findings—Our laboratory demonstrated that intradialytic hypertension occurs at least sporadically in most hemodialysis patients, but in 25% of patients it occurs in over 31% of their hemodialysis treatments. We also identified that compared to hemodialysis patients without intradialytic hypertension, those with intradialytic hypertension have worse endothelial cell function and have higher interdialytic ambulatory blood pressure. Pilot study data shows that carvedilol reduces the frequency of intradialytic hypertension and improves endothelial cell dysfunction.

Summary—Intradialytic hypertension is associated with increased morbidity and mortality, impaired endothelial cell function, and higher overall blood pressure burden. Further investigation is required to determine if interventions aimed at preventing or treating intradialytic hypertension improve long term outcomes.

Keywords

Hemodialysis; Hypertension; Intradialytic Hypertension; Endothelial Cell Dysfunction; Ambulatory Blood Pressure

INTRODUCTION

End-stage renal disease (ESRD) patients on hemodialysis (HD) have nearly a 20% annual mortality rate, with cardiovascular (CV) death being the primary cause [1]. The prevalence

Corresponding Author: Peter Van Buren, 5939 Harry Hines Boulevard, Dallas, TX 75390-8523, Phone: 214-645-8267, Fax: 214-645-8903, Peter.vanburen@phhs.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The work was presented in part as an oral presentation at the Southern Society of Clinical Investigation Nephrology Young Investigator Forum February 16, 2011 and at the National Kidney Foundation 6th Annual Nephrology Young Investigator Forum April 26, 2011 in Las Vegas, NV.

CONFLICTS OF INTEREST: There are no conflicts of interest to disclose.

of hypertension is nearly 90% in these patients, and it is associated with increased CV morbidity and mortality [2, 3]. However, the linear relationship between increasing systolic BP and increasing CV mortality that exists in the general population[4] does not exist in HD patients. In fact, a U-shaped curve defines the relationship between single HD-unit BP measurements and mortality[5]. It is known that home and ambulatory BP measurements from the interdialytic time period are better predictors of mortality than individual pre or post-HD BP measurements[6]. Interdialytic BP measurements are considered the gold standard for assessing overall BP burden and risk for catastrophic outcomes in HD patients. Unfortunately cost and patient non-adherence may limit clinical use of such measurements. Therefore, it is essential to be able to identify patients at the highest risk for adverse clinical outcomes based on clinical data obtained in the HD unit.

Recent attention has been directed to the significance of BP changes during a HD treatment. While most HD patient sex hit a decrease in BP during HD, some patients experience an increase in BP, commonly referred to as intradialytic hypertension. When defined as an increase in systolic BP ≥ 10 mmHg from pre to post-HD, intradialytic hypertension has been associated with increased morbidity and mortality in prevalent and incident HD populations[7,8]. Our laboratory has focused on identifying potential new mechanisms underlying hypertension among patients on maintenance HD and the association of intradialytic hypertension with adverse outcomes[9•]. The purpose of this article is to present our current understanding of the epidemiology and potential mechanisms of intradialytic hypertension and to discuss the relationship between intradialytic hypertension and ambulatory BP.

DEFINITION AND EPIDEMIOLOGY

We define intradialytic hypertension specifically as an increase in systolic BP from pre to post-HD ≥ 10 mmHg. Others have defined intradialytic hypertension as an increase in mean arterial pressure ≥ 15 mmHg during or at the end of a HD treatment[10–13]. Intradialytic BP changes have also been analyzed using regression analysis of all BP measurements during the course of an HD treatment[14••]. However, the definition of a 10 mmHg increase in systolic BP from pre to post-HD is the only definition that has been associated with increased morbidity and mortality in the HD patients and thus has proven clinical relevance[7,8].

The reported prevalence of intradialytic hypertension varies depending on the number of HD treatments in which BP measurements are ascertained. In retrospective analysis of the Crit Line Intradialytic Monitoring Benefit (CLIMB) study, 13.2% of these prevalent HD patients had average systolic BP increases ≥ 10 mmHg from pre to post-HD when assessed over 4 HD treatments[7]. Using this same definition, when HD-unit BP measurements were assessed over 2 weeks, another study reported 12.2% of incident HD patients had intradialytic hypertension[8]. We recently found during a 6-month assessment of all pre and post-HD BP measurements taken during the course of routine HD treatments in another HD cohort, that intradialytic hypertension occurred in 21.3% of all treatments[15•]. In this observational study, almost every patient encountered at least one episode of intradialytic hypertension over 6 months, but it occurred in $>31\%$ of the treatments in the quartile of patients that encountered it most often.

SUGGESTED MECHANISMS

The proposed etiologies of intradialytic hypertension have been previously reviewed[16•, 17•] and are summarized in Table 1. Table 2 details the results of studies that have addressed these etiologies[11–13, 14••, 18, 19, 20••]. Taken together, the available evidence points to endothelial cell dysfunction (Figure 1) and volume overload as the most likely causes.

Endothelial Cell Dysfunction

Endothelial cell dysfunction entails an imbalance in the release of vasoconstrictors and vasodilators from the endothelial cells that favors vasoconstriction. Initial associations between endothelial cell dysfunction and intradialytic hypertension came from case-control studies that showed increases in plasma endothelin-1 (a potent vasoconstrictor) along with decreases in serum nitric oxide (a potent vasodilator) during HD in patients with intradialytic hypertension[11,12]. More recently, Inrig et al. have demonstrated that compared to HD controls, patients with intradialytic hypertension have decreased circulating plasma endothelial progenitor cells measured before HD and lower flow-mediated vasodilation measured on non-HD days[20•]. These findings indicate a reduced capacity for endothelial cell repair and an inadequate response of the endothelium to shear stress, respectively. Although underlying endothelial cell dysfunction could potentially explain adverse outcomes during follow-up, it remains unclear how the HD procedure impacts the balance of vasodilators and vasoconstrictors resulting in intradialytic BP increases. Anecdotally, Fourtounas found that intradialytic BP increases were attenuated during treatments with isolated ultrafiltration compared to ordinary HD treatments[21•]. The author suggested that exposure to dialysate was responsible for this “malignant intradialytic hypertension.” While differences in pre and post-HD plasma calcium or potassium have not been observed[12] in patients with intradialytic hypertension compared to HD controls, the role of the dialysate sodium concentration remains an area of interest. Previously, nephrologists used dialysate with sodium concentrations that were lower than patients’ pre-HD serum sodium concentration to facilitate sodium removal via diffusion. This strategy became unnecessary after HD machines became equipped with directly programmable ultrafiltration to remove larger amounts of sodium in short periods of time via convection. To avoid decreases in BP that might result from rapid removal of fluid, higher dialysate sodium concentration became more common. However, in situations where the dialysate sodium concentration exceeds a patient’s pre-HD serum sodium concentration, the sodium gradient presents a risk for a net positive sodium transfer mediated by diffusion. In the case-control study reported by Inrig et al., there was a trend towards lower pre-HD serum sodium in patients with intradialytic hypertension compared to controls[20•]. Beyond the potential volume-related implications of sodium transfer during HD, in vitro evidence suggests that high sodium concentrations may induce endothelial cell “stiffening” with impaired release of nitric oxide resulting in unopposed vasoconstriction[22]. Our laboratory is currently investigating the effects of different dialysis prescriptions on intradialytic hypertension in a clinical trial[23•].

Volume Overload

The earliest reports of intradialytic hypertension came from small uncontrolled studies in patients with echocardiographic abnormalities including left ventricular dilatation. These studies identified volume overload as the responsible mechanism[18,19]. With initiation of HD and ultrafiltration there was a reduction in end-diastolic volume and an increase in cardiac output, which manifest as an increase in BP. However, with more aggressive ultrafiltration, cardiac output and BP decreased concomitantly. In contrast, a case-control study showed that cardiac output decreased from pre to post-HD in all patients, but patients with intradialytic hypertension experienced a greater increase in vascular resistance[12].

No study has directly measured extracellular volume in patients with intradialytic hypertension; however, the impact of interdialytic weight gain has been assessed. Interdialytic weight gain is positively correlated with higher pre-HD systolic BP and with greater reductions in BP during HD[24]. We have furthermore shown that lower interdialytic weight gain and ultrafiltration volume are both associated with increased occurrences of intradialytic hypertension[25•]. Recent retrospective analysis from the dry weight reduction

in hypertensive hemodialysis patients (DRIP) study showed that slowly reducing estimated dry weight over several weeks lowered interdialytic BP and caused greater reductions in intradialytic BP, although most of these patients already had intradialytic BP decreases prior to this intervention[14•]. The findings from these studies highlight the need for more validated assessments of extracellular volume in the context of intradialytic hypertension.

RELATIONSHIP TO AMBULATORY BLOOD PRESSURE

Higher average interdialytic ambulatory BP predicts mortality in HD patients[6]. In general, individual HD-unit BP measurements lack precision in estimating ambulatory BP[26]. Inclusion of multiple intradialytic BP measurements in addition to pre and post-HD measurements improves the accuracy of diagnosing HTN as compared to pre or post-HD measurements alone[27]. Thus, it is clear that the relationship between ambulatory BP and intradialytic BP measurements is strengthened by including more than a single HD-unit measurement.

However, these findings do not specifically address the relationship between the *intradialytic BP pattern* and ambulatory BP. Because intradialytic HTN has been associated with increased morbidity and mortality, it is important to know how increases in BP during HD relate to BP measurements during the interdialytic period. We recently reported the results of a case-control study examining the relationship between intradialytic hypertension and ambulatory BP[28•]. All patients in this study had pre-HD systolic BP >140 mmHg or post-HD systolic BP >130 mmHg during a 2-week screening period. Cases (n=25) were those with systolic BP increases from pre to post-HD ≥ 10 mmHg in $\geq 4/6$ screening HD treatments, and controls were those with systolic BP decreases ≥ 10 mmHg in $\geq 4/6$ screening HD treatments[28•]. The average 44-hr ambulatory systolic BP was significantly higher (155.4 vs 142.4 mmHg) in patients with intradialytic hypertension compared to controls. This elevated BP persisted after performing individual analyses of daytime and nocturnal systolic and diastolic BP. A “non-dipping” nocturnal BP pattern was almost universal in the study (98% of cases, 100% of controls). There were strong correlations with interdialytic BP and both pre and post-HD BP. The strongest correlation with interdialytic BP for both groups was with the average of pre and post-HD BP. In addition to the difference in average ambulatory BP, there was also a demonstrable difference in the *ambulatory BP pattern*. During the first 24 hours after HD, systolic BP was higher in those with intradialytic hypertension as compared to controls, but demonstrated a decreasing trend over time. After 24 hours, BP increased among patients with intradialytic hypertension until shortly before the next HD treatment. In contrast, the BP of the control group had a gradual increase from the first hour after HD until shortly before the next treatment (Figure 2).

The ambulatory BP pattern in the control group is consistent with what had previously been reported in HD patients between treatments[29]. The discrepancy between the two patterns in the case-control study suggests that patients with intradialytic hypertension may be less salt sensitive during the initial period after HD, and that other factors such as vasoconstriction may be predominantly responsible for the elevated BP during this time.

In a previous analysis of interdialytic BP in HD patients, arterial stiffness and interdialytic weight gain modified the BP pattern between treatments[30]. Specifically, greater arterial stiffness was associated with a higher intercept (post-HD BP) for a given amount of weight gain. Greater interdialytic weight gain was associated with a greater slope or hourly increase in BP for a given level of arterial stiffness. Retrospective analysis of the DRIP study demonstrated that gradual reduction in dry weight results in a *lower* post-HD BP, but an *increased* interdialytic BP slope[31]. However, in all of these scenarios there remained a

rather consistent increase insystolic BP during the 44 hour interdialytic period which did not occur among our patients with intradialytic hypertension (Figure 2).

Finally, the impact of specific antihypertensives on ambulatory BP patterns remains unclear. In our case-control cohort, more patients with intradialytic hypertension were taking angiotensin-converting enzyme (ACE)-inhibitors than controls, but there was no difference in overall use of ACE-inhibitors or angiotensin receptor blockers between groups. All patients receiving ACE-inhibitors were either on lisinopril or quinapril. Both of these medications are potentially dialyzable and may have modified both the intradialytic BP and the interdialytic BP for several hours after the treatment.

CURRENT RECOMMENDATIONS

Our data demonstrate that intradialytic hypertension is associated with an overall increased interdialytic BP burden. While greater awareness of this subpopulation is warranted, there is insufficient evidence to indicate that deviating from the current recommendations for treating hypertension in the general HD population is necessary. As with all HD patients, identifying and achieving dry weight is essential. Dry weight reduction lowers intradialytic and interdialytic BP in most HD patients[14••]. However, pharmacologic antihypertensive therapy is still often necessary and has been associated with a mortality benefit in HD patients[32,33]. While inhibitors of the renin-angiotensin aldosterone system are considered first line agents for HD patients, it is important to recognize differences in the dialyzability of antihypertensive drugs.

Antihypertensive selection for specific comorbidities in HD patients and the dialyzability of various drugs are provided in a recent review[34]. The benefits of switching from a dialyzable antihypertensive to a non-dialyzable drug remain uncertain regarding the overall effects on intra/interdialytic BP or morbidity/mortality. Early results of the Mechanisms and Treatment of Intradialytic Hypertension Study[9•] (NCT00827775) suggest carvedilol to be a good therapeutic option among those with intradialytic hypertension. In this prospective open-label study of carvedilol among 25 HD patients with intradialytic hypertension, chronic oral administration of carvedilol, an antihypertensive agent which has been shown to lower endothelin-1, improved both endothelial cell function and reduced the frequency of intradialytic hypertension[35•].

FUTURE DIRECTIONS

The higher average ambulatory BP in patients with intradialytic hypertension provides a potential explanation for the increased risk for adverse events observed among these patients, but the differences in the ambulatory BP pattern remain intriguing and unexplained to date. This concept has relevance to the more generalizable HD population as well. While the average of ambulatory BP measurements predicts mortality in HD patients, it is unknown if prolonged periods of moderately elevated BP or intermittent periods of severely elevated BP during the interdialytic interval are associated with greater morbidity and mortality. Although limited by only 24 hours of post-HD ambulatory BP measurements, one cross-sectional study found no difference in left ventricular hypertrophy in patients who were hypertensive during and 24 hours after HD and patients with normal post-HD BP but steady increases in BP to the hypertensive level for the next 24 hours[36]. Understanding the underlying mechanisms responsible for BP elevations throughout the entire interdialytic time period would facilitate a more targeted approach to BP management in HD patients. In short, the method of achieving lower average ambulatory BP, the gold standard for assessing risk in HD patients, may depend on what factors are influencing the interdialytic BP at different points in time. For patients with intradialytic hypertension the components of both extracellular volume and increased vasoconstriction from endothelial cell dysfunction

should be considered. Finally, it remains unknown how differences in the hourly interdialytic BP affect outcomes in HD patients with or without intradialytic hypertension.

CONCLUSIONS

Intradialytic hypertension is an under recognized marker of increased risk for morbidity and mortality among maintenance HD patients. Endothelial cell dysfunction appears to be a major mechanism underlying this phenotype, and the role of extracellular volume overload remains to be better defined. Patients with intradialytic hypertension have higher ambulatory BP than other HD patients. The differences in the ambulatory hourly BP patterns between the groups warrant a closer examination of how endothelial cell dysfunction and volume overload impact interdialytic BP patterns in all HD patients. Whether prevention or treatment of intradialytic hypertension improves outcomes in this high risk group is an important clinical question that requires further investigation.

Key Points

- Intradialytic hypertension, defined as an increase in systolic blood pressure from pre to post-dialysis ≥ 10 mmHg, is associated with increased morbidity and mortality in incident and prevalent HD patients.
- Intradialytic hypertension has recently been associated with underlying endothelial cell dysfunction, supporting prior evidence of increases in plasma ET-1 during hemodialysis in these patients.
- Patients with intradialytic hypertension have higher average ambulatory systolic blood pressure compared to hemodialysis patients with decreases in blood pressure from pre to post-dialysis.
- The ambulatory systolic blood pressure tends to decrease during the initial 24 hours of the interdialytic time period, deviating from the typical increase observed in most hemodialysis patients.
- Beyond the current recommendations for managing hypertension in all hemodialysis patients, which includes achieving dry weight and adding pharmacologic therapy as necessary, there is insufficient evidence for additional recommendations in patients with intradialytic hypertension at this point.

Acknowledgments

Sources for funding: This work was supported by the UT Southwestern O'Brien Center, NIH UT Southwestern Clinical Translational Science Award (UL1RR024982), NIH grant K23 HL092297 (JKI), NIH grant F32DK085965-O1A1 (PVB), and NIH grant K24DK002818-06.

REFERENCES

1. United States Renal Data System. USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States. 2010 Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and finding of these data are the responsibility of the author and in no way should be seen as an official policy or interpretation of the U.S. government.
2. Foley RN, Parfrey PS, Harnett JD, et al. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int.* 1996; 49:1379–1385. [PubMed: 8731103]

3. Agarwal R, Nissenson A, Battle D, et al. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med.* 2003; 115:291–297. [PubMed: 12967694]
4. Lewington S, Clarke R, Qizilbash N, et al. Age specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002; 360:1903–1913. [PubMed: 12493255]
5. Li Z, Lacson E, Lowrie E, et al. The Epidemiology of Systolic Blood Pressure and Death Risk in Hemodialysis Patients. *Am J Kidney Dis.* 2006; 48:606–615. [PubMed: 16997057]
6. Alborzi P, Patel N, Agarwal R. Home Blood Pressures Are of Greater Prognostic Value than Hemodialysis Unit Recordings. *Clin J Am Soc Nephrol.* 2007; 2:1228–1234. [PubMed: 17942773]
7. Inrig J, Oddone E, Hasselblad V, et al. Association of intradialytic blood pressure changes with hospitalization and mortality rates in prevalent ESRD patients. *Kidney Int.* 2007; 71:454–461. [PubMed: 17213873]
8. Inrig J, Patel N, Toto R, Szczech LA. Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: a secondary analysis of the Dialysis Morbidity and Mortality Wave 2 Study. *Am J Kidney Dis.* 2009; 54:881–890. [PubMed: 19643520]
9. National Heart, Lung, and Blood Institute (NHLBI). The University of Texas Southwestern Medical Center at Dallas. Mechanism and Treatment of Intradialytic Hypertension. ClinicalTrials.gov [Internet]. 2000[cited October 27 2010] Bethesda (MD) National Library of Medicine (US) Available from <http://clinicaltrials.gov/ct2/show/NCT00827775>. NLM Identifier NCT 00827775 • This is the clinicaltrials.gov entry for the MATCH study. This was a case-control study of patients with intradialytic hypertension (defined as an increase in systolic blood pressure from pre to post-hemodialysis greater than 10 mmHg in more than 4/6 screening treatments) and hemodialysis controls (systolic blood pressure decreases from pre to post-dialysis). At baseline, measurements were obtained for endothelial cell function (pre-hemodialysis plasma levels of endothelial progenitor cells and non-dialysis day shear stress induced flow mediated vasodilation), ambulatory blood pressure, and pulse wave velocity. Following this, an uncontrolled pilot study was conducted in the intradialytic hypertension subjects where they were started on carvedilol and titrated up to the maximally tolerated dose. This dose was continued for 4 additional weeks and all baseline measurements were repeated following the treatment period.
10. Amerling, R.; Dubrow, A.; Levin, N.; Osherooff, R., et al. Complications during hemodialysis. Stamford: Appleton and Lange; 1995.
11. Raj D, Vincent B, Simpson K, et al. Hemodynamic changes during hemodialysis: Role of nitric oxide and endothelin. *Kidney Int.* 2002; 61:697–704. [PubMed: 11849413]
12. Chou K, Lee P, Chen C, et al. Physiologic changes during hemodialysis in patients with intradialysis hypertension. *Kidney Int.* 2006; 69:1833–1888. [PubMed: 16691262]
13. El Shafey E, El Nagar G, Selim M, El-Sorogy H, Sabry A. Is there a role for endothelin-1 in the hemodynamic changes during dialysis? *Clin and Exp Nephrology.* 2008; 12:370–375.
14. Agarwal R, Light R. Intradialytic hypertension is a marker of volume excess. *Nephrol Dial Transplant.* 2010; 25:3355–3361. [PubMed: 20400448] •• This was a retrospective analysis of the DRIP study which demonstrated that dry weight reduction resulted in decreased ambulatory blood pressure as well as a greater slope of intradialytic blood pressure decrease. Of note, at baseline the average intradialytic change in systolic blood pressure was a decrease of approximately 3 mmHg/hour, and most subjects did not have intradialytic hypertension. However, this study emphasizes how most hemodialysis patients respond to changes in dry weight. Additionally, this study introduces the analysis of intradialytic blood pressure measurements using regression analysis.
15. Van Buren P, Kim C, Toto R, Inrig J. Prevalence of Recurrent Intradialytic Hypertension. *Am J Kidney Dis.* 2011; 57:B100. • This abstract was a poster presentation at the National Kidney Foundation Spring Clinical Meeting in April 2011. This demonstrated the overall prevalence and intraindividual incidence of intradialytic hypertension (defined as an increase in systolic blood pressure greater than 10 mmHg from pre to post-hemodialysis) in a hemodialysis cohort over the course of 6 months.
16. Inrig JK. Intradialytic hypertension: a less-recognized cardiovascular complication of hemodialysis. *Am J Kidney Dis.* 2010; 55:580–589. [PubMed: 19853337] • This is an excellent review that discusses the epidemiology and proposed pathophysiology of intradialytic

hypertension, as well as its association with adverse events based on information available prior to this review period.

17. Chazot C, Guillaume J. Intradialytic Hypertension: It Is Time To Act. *Nephron Clinical Practice*. 2010; 115:182–188. •This is another excellent review on intradialytic hypertension.
18. Cirit M, Akcicek F, Terzioğlu E, et al. "Paradoxical" rise in blood pressure during ultrafiltration in dialysis patients. *Nephrol Dial Transplant*. 1995; 10:1417–1420. [PubMed: 8538935]
19. Gunal A, Karaca I, Celiker H, Ikay E, Duman S. Paradoxical rise in blood pressure during ultrafiltration is caused by increased cardiac output. *J Nephrol*. 2002; 15:42–47. [PubMed: 11936425]
20. Inrig J, Van Buren P, Kim C, Vongpatanasin W, Povsic T, Toto R. Intradialytic Hypertension and Endothelial Cell Dysfunction. *Clin J Am Soc Nephrol*. 2011 (in press). ••This manuscript discusses the results of the baseline endothelial cell dysfunction measurements in the MATCH study (see ref 9). While previous evidence showed intradialytic increases in endothelin-1 in patients with intradialytic hypertension, this study shows that patients with intradialytic hypertension have greater underlying endothelial cell dysfunction that can be appreciated outside the context of the hemodialysis procedure.
21. Fourtounas C. "Malignant" intradialytic hypertension: a severe form of intradialytic hypertension. *Am J Kidney Dis*. 2010; 56:418. [PubMed: 20659627] •This letter was published in *AJKD* documenting one nephrologist's experience with intradialytic hypertension. This shows how that intradialytic increases in blood pressure were of lower magnitude during treatments with ultrafiltration only, suggesting that a component of the dialysate may contribute to intradialytic hypertension.
22. Oberleithner H, Riethmüller C, Schillers H, MacGregor G, de Wardener H, Hausberg M. Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. *Proc Natl Academy of Sciences USA*. 2007; 104:16281–16286.
23. University of Texas Southwestern Medical Center. Mechanisms and Treatment of Intradialytic Hypertension-Sodium (MATCH-Sodium). *ClinicalTrials.gov* [Internet]. 2011 cited June 10 2011 Bethesda (MD) National Library of Medicine (US) Available from <http://www.clinicaltrials.gov/ct2/show/NCT01371890>. NLM Identifier NCT 01371890 •This is the clinicaltrials.gov website for the MATCH-Sodium study that is currently underway. This is a crossover study in patients with intradialytic hypertension to determine the association between intradialytic serum sodium levels and intradialytic hypertension while being exposed to regular dialysis (dialysate + ultrafiltration), dialysate only, or ultrafiltration only.
24. Inrig JK, Patel UD, Gillespie BS, et al. Relationship between interdialytic weight gain and blood pressure among prevalent hemodialysis patients. *Am J Kidney Dis*. 2007; 50:108–118. 18 e1-4. [PubMed: 17591530]
25. Van Buren P, Toto R, Inrig J. Effect of Interdialytic Weight Gain on Intradialytic Hypertension. *J Investigative Med*. 2011; 59:372–544. •This abstract was presented as an oral presentation at the Southern Society of Clinical Investigation Nephrology Young Investigator Forum, February 15, 2011 in New Orleans, LA and at the National Kidney Foundation Spring Clinical Meeting Nephrology Young Investigator Forum, April 26, 2011 in Las Vegas Nevada. This study showed that there was a negative association between the occurrence of intradialytic hypertension and both interdialytic weight gain and ultrafiltration volume when each treatment over the course of 6 months was analyzed.
26. Agarwal R, Peixoto A, Santos S, Zoccali C. Pre and Postdialysis Blood Pressure Are Imprecise Estimates of Interdialytic Ambulatory Blood Pressure. *Clin J Am Soc Nephrol*. 2006; 1:389–396. [PubMed: 17699236]
27. Agarwal R, Metiku T, Tegegne G, et al. Diagnosing Hypertension by Intradialytic Blood Pressure Recordings. *Clin J Am Soc Nephrol*. 2008; 3:1364–1372. [PubMed: 18495949]
28. Van Buren P, Kim C, Toto R, Inrig J. Intradialytic Hypertension and the Association With Interdialytic Ambulatory Blood Pressure. *Clin J Am Soc Nephrol*. 2011; 6:1684–1691. [PubMed: 21734087] ••This manuscript reports the ambulatory blood pressure findings from the MATCH study (see ref 9). This reports that average ambulatory blood pressure was 13 mmHg higher in subjects with intradialytic hypertension compared to hemodialysis controls. Furthermore it demonstrated different interdialytic blood pressure *patterns* between the 2 groups.

29. Kelley K, Light R, Agarwal R. Trended Cosinor Change Model for Analyzing Hemodynamic Rhythm Pattern In Hemodialysis Patients. *Hypertension*. 2007; 50:143–150. [PubMed: 17515445]
30. Agarwal R, Light RP. Arterial stiffness and interdialytic weight gain influence ambulatory blood pressure patterns in hemodialysis patients. *Am j Physiol Renal Physiol*. 2008; 294:F303–F308. [PubMed: 18160623]
31. Agarwal R. Volume-associated ambulatory blood pressure patterns in hemodialysis patients. *Hypertension*. 2009; 54:241–247. [PubMed: 19528362]
32. Heerspink H, Ninomiya T, Zoungas S, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomized controlled trials. *Lancet*. 2009; 373:1009–1015. [PubMed: 19249092]
33. Agarwal R, Sinha A. Cardiovascular Protection With Antihypertensive Drugs in Dialysis Patients: Systematic Review and Meta-Analysis. *Hypertension*. 2009; 53:860–866. [PubMed: 19273737]
34. Inrig J. Antihypertensive Agents in Hemodialysis Patients: A Current Perspective. *Seminars in Dialysis*. 2010; 23:290–297. [PubMed: 20374548]
35. Inrig J, Van Buren P, Kim C, Toto R. Carvedilol for the Treatment of Intradialytic Hypertension: The Mechanisms and Treatment of Intradialytic Hypertension (MATCH) Study. *Journal of Clin Hypertension*. 2011; 13:A4–A5. • This abstract was presented as an oral presentation at the American Society of Hypertension 26th Annual Meeting 2011. This reports the results of the pilot portion of the MATCH study (see ref 9). This demonstrated that following treatment with carvedilol, intradialytic hypertension patients had decreased ambulatory blood pressure, decreased incidence of intradialytic hypertension, and improvement in flow mediated vasodilation.
36. Cannella G, Paoletti E, Ravera G, et al. Inadequate diagnosis and therapy of arterial hypertension as causes of left ventricular hypertrophy in uremic dialysis patients. *Kidney Int*. 2000; 58:260–268. [PubMed: 10886571]

Figure 1. Proposed mechanisms contributing to endothelial cell dysfunction in intradialytic hypertension

Vascular tone is normally balanced by the actions of endothelin-1 and nitric oxide (Box A). Nitric oxide is synthesized and released by endothelial nitric oxide synthase (eNOS) in the vascular endothelial cells. Nitric oxide binds to nitric oxide receptors on vascular smooth muscle cells, inducing vasodilation. This action is countered by the vasoconstrictive effects of endothelin 1 on endothelin A (ETA) receptors on the vascular smooth muscle cells. Bone marrow derived circulating endothelial progenitor cells repair damaged endothelial cells in order to maintain optimal endothelial function. While endothelial cell dysfunction exists in most HD patients, it is more severe in patients with intradialytic hypertension (Box B). Patients with intradialytic hypertension have decreased levels of plasma circulating endothelial progenitor cells suggesting dysfunctional repair of damaged endothelial cells. Furthermore, these patients have impaired flow mediated vasodilation measured on non-HD days compared to HD controls indicating greater underlying endothelial cell dysfunction. During the HD procedure, patients with intradialytic hypertension have increases in plasma endothelin-1 and decreases in serum nitric oxide, favoring overall vasoconstriction. It is hypothesized that increases in the serum sodium concentration induced by sodium diffusion from the dialysate may cause endothelial cell dysfunction by causing “stiffening” of endothelial cells, resulting in impaired release of nitric oxide.

Figure 2. Average Hemodialysis Unit Pre and Post-Hemodialysis Systolic Blood Pressure and Hourly Ambulatory Systolic Blood Pressure in Intradialytic Hypertension Patients and Hemodialysis Controls

On the left (A and B) are the pre and post-hemodialysis unit systolic blood pressure measurements averaged over 2 weeks that were reported in a recent case-control study (Van Buren *Clin J Am Soc Nephrol*, 2011). Systolic blood pressure increases from pre to post-dialysis in patients with intradialytic hypertension (A), and it decreases in hemodialysis controls (B). On the right (C and D) are plots of the ambulatory systolic blood pressure during each hour of the interdialytic time period. In patients with intradialytic hypertension, there is a trend towards a decrease in ambulatory blood pressure for the initial 24 hours, after which the blood pressure increases until the next hemodialysis treatment (C). In the

hemodialysis controls, the systolic ambulatory blood pressure increases during the entire interdialytic time period (D).

Table 1

Proposed Etiologies of Intradialytic Hypertension

Extracellular Volume Overload
Endothelial Cell Dysfunction
Activation of the Sympathetic Nervous System
Activation of the Renin Angiotensin Aldosterone System
Removal of Antihypertensives During Hemodialysis
Electrolyte Changes Induced by the Dialysate Composition

Table 2

Proposed Etiologies of Intradialytic Hypertension and Related Clinical Studies

Proposed Pathogenesis	Author	Subjects/Design	Endpoint	Results	Limitations
Excessive Extracellular Volume	Girit 1995 [18]	Uncontrolled study n=7 HD subjects with BP increases during HD despite ultrafiltration Observation period Vs. Intensified ultrafiltration + dietary sodium restriction	Average systolic BP change from pre to post-HD (mmHg) Observation period: Intense Ultrafiltration period:	+32 mmHg -46 mmHg	Uncontrolled study, small sample size
	Gunal 2002 [19]	Uncontrolled study n=6 subjects with BP increases during HD	Cardiac Index (L/min/m ²) Mean arterial pressure (mmHg)	After 2520 mL ultrafiltration: 4.8 L/min/m ² (3.8 at baseline) After 4133 mL ultrafiltration: 3.1 L/min/m ² (from 4.8) After 2520 mL ultrafiltration: increase to 118 mmHg (107 mmHg at baseline) After 4133 mL ultrafiltration: BP normalized	Uncontrolled study, small sample size
	Agarwal 2010 [14]	Retrospective analysis of randomized clinical trial n=100 prevalent HD subjects with dry weight probed over 8 weeks vs. 50 prevalent HD subjects with no change in prescription	Change in slope of systolic BP change (%) Ultrafiltration vs. control at 4 weeks 8 weeks	0.38%/hr (p=0.2) 0.84%/hr (p=0.035) Each %/hr increase in intradialytic slope associated with 0.71 mmHg reduction in ambulatory systolic BP (p=0.048)	Not designed to study intradialytic hypertension (average baseline slope of intradialytic systolic BP was decrease of approximately 3%/hr in both groups).
Endothelial Cell Dysfunction	Raj 2002 [11]	Case-control study n=27 HD patients Group 1: stable BP	Endothelin-1 (pg/mL) Group 1: Pre-HD Post-HD	14.3 15.0 (p=NS vs. pre) 12.0 8.7 (p<0.05 vs. pre) (p<0.001 vs. post-HD)	

Proposed Pathogenesis	Author	Subjects/Design	Endpoint	Results	Limitations
		Group II: BP decreases during HD Group III: BP increases during HD	Group II: Pre-HD: Post-HD: Group III: Pre-HD: Post-HD: Fractional Exhaled nitric oxide (ppb) Group I: Pre-HD: Post-HD: Group 2: Pre-HD: Post-HD: Group 3: Pre-HD: Post-HD:	in Groups 1 and 3) 12.8 16.7 (p=0.06 vs. pre) 17.8 19.9 (NS vs. pre) 24.1 (p<0.05 vs. other groups) 23.1 (NS vs. pre) 16.1 21.7 (NS vs. pre)	
	Chou 2006 [12]	Case-control study n=30 Intradialytic Hypertension and 30 HD controls	Nitric Oxide (µM) IH subjects: Pre-HD Post-HD Control: Pre-HD Post-HD Endothelin-1 (pg/ml) IH subjects: Pre-HD Post-HD Controls: Pre-HD Post-HD Nitric Oxide/Endothelin-1 IH: Pre-HD Post-HD Controls: Pre-HD Post-HD	41.2 7.2 (p<0.005 vs. pre) 32.9 7.9 (p<0.005 vs. pre) (NS when compared to IH group) 345.6 510.9 (p<0.005 vs. pre) 287.4 276.7 (NS vs. pre) (p<0.05 compared to IH group) 0.869 0.018 (p<0.005 vs. pre) 0.129 0.034 (p<0.005 vs. pre) (p<0.05 compared to IH group)	
	El Shafey 2008 [13]	Case-Control Study n=45 HD subjects Group 1: stable intradialytic BP Group 2: Intradialytic BP decreases Group 3: Intradialytic BP increases	Endothelin-1: (pg/mL) Group 1: Pre-HD Post-HD Group 2: Pre-HD Post-HD Group 3: Pre-HD Post-HD	14.33 14.49 (NS vs. pre) 11.75 8.65 (p<0.001 vs. pre) (p<0.001 vs. groups I and II) 11.93 16.39 (p<0.001 vs. pre)	

Proposed Pathogenesis	Author	Subjects/Design	Endpoint	Results	Limitations
	Inrig 2011 [20]	Case-Control Study n=25 IH patients n=25 prevalent HD controls	Endothelial Progenitor Cells (IH vs control); ALDH ^{br} CD34 ⁺ CD133 ⁺ Flow Mediated Vasodilation (%) (IH vs control);	0.034% vs. 0.052% (p=0.03) 0.033% vs. 0.059% (p=0.03) 1.03% vs. 1.67% (p=0.02)	
RAAS Activity	Chou 2006 [12]	30 IH patients 30 HD controls	Plasma Renin (pg/ml) IH Pre-HD Post-HD Controls Pre-HD Post HD	10.8 10.6 (NS vs. pre) 15.1 24.9 (p<0.05 vs. pre) (p<0.05 compared to IH group)	Goes against hypothesis
Sympathetic Nervous System Activity	Chou 2006 [12]	30 IH patients 30 HD controls	Plasma epinephrine (pg/ml) IH: Pre-HD; Post-HD Controls; Pre-HD; Post-HD; Plasma norepinephrine (pg/ml) IH: Pre-HD; Post-HD; Controls; Pre-HD; Post-HD;	97.1 87.6 (NS vs. pre) 99.0 100.4 (NS vs. pre) (NS compared to IH group) 225 204 (NS vs. pre) 253 363 (p<0.05 vs. pre) (p<0.05 compared to IH group)	Goes against hypothesis
Removal of antihypertensives		No study available			
Electrolyte Changes		No study available			

HD-Hemodialysis, BP-Blood Pressure, ABP-Ambulatory Blood Pressure, IH-Intradialytic Hypertension