It is important to recognize that, although intuitively appealing, we do not really know from animal or human studies if treatments that reduce neointimal hyperplasia will actually translate into improved outcomes for AVFs. Neointimal hyperplasia and stenosis formation may accompany other contributors to maturation failure, such as inadequate vessel dilation, or they may even be a consequence rather than a cause of maturation failure. A next step for Wang *et al.*[4] in their investigation of the role of Notch blockade could be measurement of AVF blood flow to determine whether recombination signal-binding protein for Igκ J region knockdown in CKD mice improves AVF function in addition to altering structure. Additionally, assessment of the relevance of Notch pathway activation to humans with CKD might be possible using primary cultures of endothelial cells obtained from patients at the time of AVF creation to perform the mesenchymal cell marker expression studies and endothelial cell barrier function assays, which were performed in the work by Wang *et al.*[4] using mouse cells.

Through a series of elegant experiments that incorporated *in vivo* and *in vitro* studies, surgical creation of mouse AVFs, genetic manipulation combined with CKD, and examination of AVF tissue from patients, Wang *et al.*[4] have made a strong case for the involvement of Notch in neointimal formation after AVF creation. Although additional work is needed to clarify the clinical and therapeutic implications of the findings, Wang *et al.*[4] should be congratulated on the necessarily complex approach that they have taken to this complex biologic problem.

ACKNOWLEDGMENTS

National Institutes of Health Grant U01-DK082232 supports the work of L.M.D. Research in the laboratory of K.S. is supported by National Institutes of Health Grant R01-DK076077.

DISCLOSURES

L.M.D. is a member of the Clinical Advisory Board of Proteon Therapeutics and has received research support from Proteon Therapeutics and Shire. The laboratory of K.S. receives research support from Boehringer Ingelheim. K.S. is also on the scientific advisory board of Abbvie.

REFERENCES

1. Al-Jaishi AA, Oliver MJ, Thomas SM, Lok CE, Zhang JC, Garg AX, Kosa SD, Quinn RR, Moist LM: Patency rates of the arteriovenous fistula for hemodialysis: A systematic review and meta-analysis [published online ahead of print October 30, 2013]. *Am J Kidney Dis* doi:10.1053/j.ajkd.2013.08.023
2. Roy-Chaudhury P, Arend L, Zhang J, Krishnamoorthy M, Wang Y, Banerjee R, Samaha A, Munda R: Neointimal hyperplasia in early arteriovenous fistula failure. *Am J Kidney Dis* 50: 782–790, 2007
3. Allon M, Robbin ML, Young CJ, Deierhoi MH, Goodman J, Hanaway M, Lockhart ME, Litovsky S: Preoperative venous intimal hyperplasia, postoperative arteriovenous fistula stenosis, and clinical fistula outcomes. *Clin J Am Soc Nephrol* 8: 1750–1755, 2013
4. Wang Y, Liang A, Luo J, Liang M, Han G, Mitch WE, Cheng J: Blocking Notch in endothelial cells prevents arteriovenous fistula failure despite CKD. *J Am Soc Nephrol* 25: 773–783, 2014
5. Sharma S, Sirin Y, Susztak K: The story of Notch and chronic kidney disease. *Curr Opin Nephrol Hypertens* 20: 56–61, 2011
6. Kopan R: Notch signaling. *Cold Spring Harb Perspect Biol* 4: 4, 2012
7. High FA, Lu MM, Pear WS, Loomes KM, Kaestner KH, Epstein JA: Endothelial expression of the Notch ligand Jagged1 is required for vascular smooth muscle development. *Proc Natl Acad Sci U S A* 105: 1955–1959, 2008
8. Sirin Y, Susztak K: Notch in the kidney: Development and disease. *J Pathol* 226: 394–403, 2012

See related article, "Blocking Notch in Endothelial Cells Prevents Arteriovenous Fistula Failure Despite CKD," on pages 773–783.

Blood Pressure Variability and Dialysis: Variability May Not Always Be the Spice of Life

Jennifer E. Flythe*† and Steven M. Brunelli*‡

*Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; †Harvard Medical School, Boston, Massachusetts; and ‡DaVita Clinical Research, Minneapolis, Minnesota

J Am Soc Nephrol 25: 650–653, 2014.
doi: 10.1681/ASN.2013111237

In 1785, the great English poet William Cowper composed the famous lines, "Variety's the very spice of life, That gives it all its flavour." While Cowper was referring to the physical world, his sentiment also captures the importance of variety and variability in numerous biologic processes. Genetic variability facilitates evolution through the differential survival of the fittest. Physiologic process variability takes on many beneficial forms, including cyclical neurohormonal release, respiratory sinus variation, and nocturnal BP dipping. Cyclic variability in these evolutionary and biologic processes facilitates health. Not all variability, however, confers advantage. A growing body of evidence suggests that BP variability (BPV) portends worse outcomes in both the general and kidney disease populations.

Numerous studies in the nondialysis population have identified BPV as a risk factor for the progression of CKD,[1] stroke,[2] and death.[2,3] The mechanistic underpinnings of these associations are not fully understood but probably hinge on BPV-induced end-organ damage that may be driven, in part, by arterial system changes.[4] The finding that calcium-channel

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Steven M. Brunelli, 825 S. 8th Street, Suite 300, Minneapolis, MN 55404. Email: sbrunelli@partners.org

blockers (CCBs) ameliorate BPV in nondialysis populations lends some credence to the arterial system's central role in BPV because CCBs induce vasodilation and are associated with arterial structural remodeling.[4]

BPV is also a compelling risk factor among patients undergoing hemodialysis (HD). Given the high burden of vascular disease in HD patients and the nonphysiologic fluid and osmolar shifts inherent to the prevailing pattern of intermittent thrice-weekly HD, it is not surprising that previous studies have shown associations between BP phenomena and adverse outcomes among HD patients. For example, the absence of nocturnal dipping,[5] BP rise over the course of dialysis,[6] and visit-to-visit pre-HD BPV[7–9] have all been linked to increased death risk. In a recent analysis, Chang *et al.* demonstrated an association between visit-to-visit pre-HD BPV and death across all pre-HD BP strata, but surprisingly did not find a significant association with cardiovascular death.[9] Flythe *et al.* examined BP fluctuations *during* dialysis (*i.e.,* intradialytic BPV) and reported a link between intradialytic BPV and all-cause and cardiovascular death.[10] In a prior study, the same authors identified older age, shorter dialysis vintage, and greater ultrafiltration (rate and volume) as associated with greater intradialytic BPV.[11] Contrary to findings in the general population, neither Chang *et al.* nor Flythe *et al.* found antihypertensive agents to play a significant role in visit-to-visit or intradialytic BPV–outcome associations among HD patients.[9,11]

In this issue of *JASN*, Shafi *et al.* present further observational data linking visit-to-visit BPV and all-cause and cardiovascular morbidity and mortality.[12] In a contemporary cohort of 11,291 incident HD patients from a single dialysis organization, the authors demonstrate an association between greater predialysis systolic BPV and higher body mass index, higher calcium-phosphate product levels, and lower hemoglobin concentrations. Nonmodifiable factors, including female sex, black race, diabetes, and comorbid cardiovascular disease, were also associated with greater BPV. Most important, lower visit-to-visit BPV was associated with greater ultrafiltration volume, dry weight attainment, and antihypertensive regimens without β-blockers or renin-angiotensin system (RAS)–blocking agents. All associations persisted across strata of pre-HD BP. The authors' findings extend the existing BPV knowledge base by shedding light on the potentially protective role of non–blocker-based and non–RAS-blocking agent–based antihypertensive regimens and by elucidating yet another reason to focus on fluid removal and the attainment of dry weight.

The strengths of Shafi and colleagues' study include its large sample; inclusion of multiple important clinical, pharmacologic, and dialysis-related patient characteristics that were absent in previous analyses; and the selection of a statistically robust BPV metric. As the BPV literature has expanded, investigators have used a range of metrics to describe BP fluctuations, including SD, SD independent of the mean, average real variability, coefficient of variation, and residuals derived from generalized linear models. The BPV metric must adequately reflect BP fluctuations without overinfluence from ambient BP levels, such that the independent effects of each can be distinguished. Independence of the BPV metric from the pre-HD BP measurement is of critical importance given the strong association of pre-HD BP and outcomes.[13] To accomplish this, Shafi *et al.* fit a mixed linear effects model to the natural log of a patient's pre-HD systolic BP measurements over time and defined BPV as the SD of the model's residuals. Differences in metric definitions between Shafi and Chang and their colleagues' investigations of visit-to-visit BPV may have led to the discrepant cardiovascular mortality findings across the two studies. Chang *et al.* defined BPV using the coefficient of variation, the ratio of the SD to the mean.[9] This method also measures BPV independent of the pre-HD SBP, but it is derived from a mean BP value and thus does not account well for individual visit-to-visit fluctuations and outlying data points. Such detail is better reflected in Shafi and coworkers' non–mean-based, mixed linear model approach. Shafi and associates' rigorous statistical approach lends strong credibility to the reported outcome associations, and the authors should be commended for their efforts.

Although Shafi and colleagues' findings add to the growing body of evidence that pre-HD BP fluctuations are poor prognostic indicators, several important limitations must be considered in interpreting the results. BPV is a dynamic phenomenon that is influenced by interactions among environmental, humoral, and neural factors. Confounders of these interrelated processes must be carefully considered in interpreting outcome associations. Although the authors included many dialysis-related confounders in the adjusted models, they did not include measures of sodium balance or objective measures of volume status. A positive dialysate-to-serum sodium gradient has been associated with greater interdialytic weight gain and predialysis BP;[14] its effects on BPV *per se* have not been reported. Additionally, sodium loading may directly induce higher BP *via* nitric oxide inhibition and associated endothelin-1 rise.[15] From Shafi and colleagues' analysis, we cannot assess associations between BPV and outcomes independent of sodium balance. Improved understanding of the role of sodium balance in BPV could potentially shed light on modifiable procedural modifications, such as dialysate sodium concentration manipulation for pre-HD BPV reduction. Finally, the development of objective volume status measures to facilitate dry weight determination is critical to mitigating BPV and other harms of chronic volume expansion.

Similarly, the study does not take into account intradialytic hemodynamic measures. Episodes of intradialytic hypotension or hypertension and/or intradialytic BPV could influence interdialytic BP patterns and fluctuations. The issue of intradialytic BPV is of particular interest because Flythe *et al.* demonstrated an association between greater intradialytic BPV and greater ultrafiltration rate and volume.[11] On the other hand, Shafi *et al.* found an association between lesser pre-HD BPV and greater ultrafiltration rate and volume. Shafi and colleagues' finding might reflect the practice of stopping or reducing

ultrafiltration in hemodynamically unstable patients; this hypothesis is supported by the fact that patients in the highest BPV quartile were less likely to achieve target weight than patients in lower BPV quartiles. Therefore, the directionality of the ultrafiltration volume–visit-to-visit BPV association remains in question. Given other compelling evidence that greater peridialytic weight gains/losses are associated with adverse clinical outcomes, increasing interdialytic weight gain/ultrafiltration volume should not be pursued as a means to reduce visit-to-visit BPV unless further data become available.

Most noteworthy, Shafi *et al.* found an association between reduced BPV and non–β-blocker–based and non–RAS-based antihypertensive regimens. Unfortunately, the authors did not examine the effects of specific antihypertensive classes within these regimen categories. Of particular interest are CCBs, a class shown to reduce BPV in non-HD populations.[4] Prospective studies assessing the effect of CCBs on pre-HD BPV are needed. Such investigations should account for patient adherence to antihypertensive agents and the administration timing of antihypertensive agents with respect to treatments, two aspects acknowledged as limitations in the current study by Shafi *et al.*

In conclusion, the study by Shafi *et al.* corroborates and expands the existing evidence that greater visit-to-visit pre-HD BPV has significant prognostic value and points to some potentially modifiable practice patterns, including antihypertensive agent selection and consistent achievement of target weight. Identification of optimal therapeutic strategies to stabilize interdialytic BPV requires prospective investigations. Altering practice without the benefit of evidence accounting for important patient differences, such as sodium balance, volume status, and timing and adherence to antihypertensive agents, should be approached with caution. Although Shafi *et al.* provide valuable observational data regarding the harms of and risk factors for visit-to-visit BPV, it is now time to set our sights on interventional studies to test these associations in real time and in real patients.

Variety often is the spice of life. The rich diversity and variety that exist among HD patients and HD treatments should compel us to test putative observational associations, such as those between BPV and outcomes in the real, variable world through prospective assessments as we seek therapeutic strategies to improve HD patient outcomes.

ACKNOWLEDGMENTS

This work was conducted with the support of a KL2 Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 1KL2 TR001100-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University, its affiliated academic health care centers, or the National Institutes of Health.

DISCLOSURES

S.M.B. is an employee of DaVita Clinical Research, has received speaking honoraria from Fresenius Medical Care North America, and has served on advisory boards for Amgen and C.B. Fleet. His spouse is employed by Astra Zeneca. J.E.F. has received speaking honoraria from Dialysis Clinic Inc.

REFERENCES

1. Manios E, Tsagalis G, Tsivgoulis G, Barlas G, Koroboki E, Michas F, Alexaki E, Vemmos K, Zakopoulos N: Time rate of blood pressure variation is associated with impaired renal function in hypertensive patients. *J Hypertens* 27: 2244–2248, 2009
2. Pringle E, Phillips C, Thijs L, Davidson C, Staessen JA, de Leeuw PW, Jaaskivi M, Nachev C, Parati G, O'Brien ET, Tuomilehto J, Webster J, Bulpitt CJ, Fagard RH; Syst-Eur investigators: Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens* 21: 2251–2257, 2003
3. Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, Ito S, Hisamichi S, Imai Y: Prognostic significance of blood pressure and heart rate variabilities: The Ohasama study. *Hypertension* 36: 901–906, 2000
4. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS; ASCOT-BPLA and MRC Trial Investigators: Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 9: 469–480, 2010
5. Covic A, Goldsmith DJ, Covic M: Reduced blood pressure diurnal variability as a risk factor for progressive left ventricular dilatation in hemodialysis patients. *Am J Kidney Dis* 35: 617–623, 2000
6. Inrig JK, Patel UD, Toto RD, 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* 54: 881–890, 2009
7. Tozawa M, Iseki K, Yoshi S, Fukiyama K: Blood pressure variability as an adverse prognostic risk factor in end-stage renal disease. *Nephrol Dial Transplant* 14: 1976–1981, 1999
8. Brunelli SM, Thadhani RI, Lynch KE, Ankers ED, Joffe MM, Boston R, Chang Y, Feldman HI: Association between long-term blood pressure variability and mortality among incident hemodialysis patients. *Am J Kidney Dis* 52: 716–726, 2008
9. Chang TI, Flythe JE, Brunelli SM, Muntner P, Greene T, Cheung AK, Chertow GM: Visit-to-visit systolic blood pressure variability and outcomes in hemodialysis. *J Hum Hypertens* 28: 18–24, 2014
10. Flythe JE, Inrig JK, Shafi T, Chang TI, Cape K, Dinesh K, Kunaparaju S, Brunelli SM: Association of intradialytic blood pressure variability with increased all-cause and cardiovascular mortality in patients treated with long-term hemodialysis. *Am J Kidney Dis* 61: 966–974, 2013
11. Flythe JE, Kunaparaju S, Dinesh K, Cape K, Feldman HI, Brunelli SM: Factors associated with intradialytic systolic blood pressure variability. *Am J Kidney Dis* 59: 409–418, 2012
12. Shafi T, Sozio SM, Bandeen-Roche KJ, Ephraim PL, Luly J, St. Peter WL, McDermott A, Scialla JJ, Crews DC, Tangri N, Miskulin DC, Michels WM, Jaar BG, Herzog C, Zager PG, Meyer KB, Wu AW, Boulware LE: Predialysis systolic blood pressure variability and outcomes in hemodialysis patients. *J Am Soc Nephrol* 25: 799–809, 2014
13. Zager PG, Nikolic J, Brown RH, Campbell MA, Hunt WC, Peterson D, Van Stone J, Levey A, Meyer KB, Klag MJ, Johnson HK, Clark E, Sadler JH, Teredesai P: "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int* 54: 561–569, 1998

14. Munoz Mendoza J, Sun S, Chertow GM, Moran J, Doss S, Schiller B: Dialysate sodium and sodium gradient in maintenance hemodialysis: A neglected sodium restriction approach? *Nephrol Dial Transplant* 26: 1281–1287, 2011
15. Oberleithner H, Riethmüller C, Schillers H, MacGregor GA, de Wardener HE, Hausberg M: Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. *Proc Natl Acad Sci U S A* 104: 16281–16286, 2007

See related article, "Predialysis Systolic BP Variability and Outcomes in Hemodialysis Patients," on pages 799–809.

Fabry Disease: Dose Matters

David G. Warnock* and Michael Mauer†
*Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; and †Departments of Pediatrics and Medicine, University of Minnesota, Minneapolis, Minnesota

J Am Soc Nephrol 25: 653–655, 2014.
doi: 10.1681/ASN.2013121322

Fabry disease is an X-linked disorder resulting from mutations of the gene that encodes the lysosomal hydrolase α-galactosidase A, and leads to progressive lysosomal accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids.[1] In classically affected male patients, clinical onset occurs in childhood or adolescence and is characterized by several symptoms as well as kidney failure, cerebrovascular manifestations, heart failure, and eventually premature death.

Nephropathy is a dominant feature in Fabry disease. Proteinuria predicts and may also contribute to the progressive decline in GFR, which may eventually lead to ESRD in the third to fifth decade of life.[2] Fabry nephropathy is generally less severe in women than in men; however, heterozygous female patients with progressive kidney involvement reach ESRD at the same median age as hemizygous male patients.[3]

Enzyme replacement therapy (ERT) with recombinant α-galactosidase, including agalsidase-α (Replagal; Shire Pharmaceuticals) and agalsidase-β (Fabrazyme; Genzyme Corporation), is currently the only approved, specific treatment for Fabry disease.[4,5] ERT stabilizes or slows the progression of Fabry nephropathy in patients with Fabry disease,[6–8] especially if proteinuria can be controlled to $<$0.5 g/d.[9] Patients are treated with 1 mg/kg agalsidase-β intravenously every other week or 0.2 mg/kg agalsidase-α every other week; other than the amount of infused protein, there appears to be very little difference between the two products.[10,11] There may be differences in the response to ERT, and it appears that the 5-fold difference in the delivered dose could affect the stabilization of renal function, at least in some patients.[12,13] The issue of effective ERT dosing for Fabry disease was brought into sharp focus by an unfortunate lapse in manufacturing practices that resulted in a worldwide shortage of the Genzyme product (Fabrazyme) between June 2009 and January 2012.

In this issue of *JASN*, Weidemann and a collaborating group in Germany report their patient experiences during the period of the Fabrazyme shortage that resulted in a change of treatment regimen in many patients.[14] Systematic and complete data collections were obtained before any change in ERT dose, at the time of dosing adjustment, and 1 year after the change in dosing. This is an especially impressive effort considering that the dose reductions caused by the shortage were unanticipated and acutely imposed with very little warning. As Weidemann *et al.* fully acknowledge in their article, decisions about dosing regimens during the shortage were based on consensus-based clinical criteria and not on a randomized prospective study design, which substantially limits comparisons between the treatment arms. More severely affected patients were in the stable agalsidase-β group, and more mildly affected patients were in the agalsidase-α group. Approximately one third of the 105 patients were maintained on standard ERT dosing at 1 mg/kg every 2 weeks, whereas the remainder receiving reduced dosing of agalsidase-β (0.3–0.5 mg/kg every 2 weeks) or were switched to agalsidase-α at 0.2 mg/kg every 2 weeks.

Although patients in the standard dosing group remained stable, patients in the dose reduction group self-reported worsened pain attacks, pain crises, and disease severity scores and patients in the switch group reported worsened pain attacks, chronic pain, gastrointestinal symptoms, and disease severity scores. The eGFR decreased by approximately 3 ml/min per 1.73 m^2 in both male and female participants in the dose reduction group and showed a similar trend in the more mildly affected switch group (P=0.09), but the eGFR was unchanged in the group maintained on standard dosing. However, the albumin/creatinine ratio increased only in the switch group. Although there were no major target organ events during the 1-year follow-up, this was a short follow-up time for such analyses and most patients had been on stable ERT dosing for at least a year before the shortage.

Two much smaller studies—with 10 patients[15] and 11 patients,[16] respectively, and with no comparison groups maintained on full dose ERT—reported no increases in symptoms or organ injury indicators 12 months after the switch to 0.2 mg/kg agalsidase-α every other week. The study by Weidemann *et al.*,[14] with very different outcomes of dose reduction, illustrates the risk of coming to potentially incorrect conclusions on the basis of statistically underpowered observations.

The licensed dose of agalsidase-β (1 mg/kg every 2 weeks) was based primarily on the findings that 20 weeks of treatment in adults substantially cleared endothelial cells of accumulated GL-3 primarily in renal peritubular capillaries, but also in the heart and skin.[4] This was sustained at 11 months although

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Michael Mauer, Departments of Pediatrics and Medicine, University of Minnesota, 2450 Riverside Avenue, East Building, MB681, Minneapolis, MN 55454. Email: mauer002@umn.edu