Title

Associations of Tissue Doppler Imaging with NT-proBNP and hs-TnT: A Pilot Study in End-Stage Renal Disease

Journal

Echocardiography, 31(10)

ISSN

0742-2822

Authors

Dubin, Ruth F
Beatty, Alexis L
Teerlink, John R
et al.

Publication Date

2014-11-01

DOI

10.1111/echo.12552

Peer reviewed

Published in final edited form as:
Echocardiography. 2014 November ; 31(10): 1205–1212. doi:10.1111/echo.12552.

Associations of Tissue Doppler Imaging with NT-proBNP and hs-TnT: A Pilot Study in End-Stage Renal Disease

Ruth F. Dubin, MD[1], **Alexis L. Beatty, MD**[2], **John R. Teerlink, MD**[2], **Nelson B. Schiller, MD**[2], **Dean Alokozai, MD**[3], and **Kirsten L. Johansen, MD**[1]

[1]Department of Medicine/Nephrology, San Francisco VA Medical Center/University of California, San Francisco

[2]Department of Medicine/Cardiology, San Francisco VA Medical Center/University of California, San Francisco

[3]Cardiocore, South San Francisco

Abstract

Background—Diastolic dysfunction is common and associated with higher mortality in the end-stage renal disease (ESRD) population. E/E', a measure derived from tissue Doppler imaging (TDI), is a correlate of left ventricular (LV) filling pressures. E/E' may be viewed as a confirmatory marker of diastolic dysfunction, but it is not routinely used to quantify diastolic dysfunction. Whether E/E' is associated with N-terminal brain natriuretic peptide (NT-proBNP) or high sensitivity troponin T (hs-TnT) in this population is not known.

Methods—We performed echocardiograms and serology prior to the 2nd or 3rd dialysis session of the week on thirty-five chronic hemodialysis patients. We compared TDI parameters (E/E' and E' alone), traditional categories of diastolic function (normal, impaired, pseudonormal or restrictive), and ejection fraction (EF) as potential predictors of the outcomes NT-proBNP and hs-TnT.

Results—Higher E/E' was associated with higher NT-proBNP (*rho* 0.48, p=0.004) and hs-TnT (*rho* 0.37, p=0.03). EF did not have statistically significant associations with NT-proBNP (*rho* -0.2, p=0.4) or hs-TnT (*rho* -0.24, p=0.16). As compared to patients with normal diastolic function, those with impaired or pseudonormal filling patterns did not have significantly different levels of NT-proBNP (p=0.46); patients in traditional categories of worsened diastolic function actually had lower hs-TnT (p=0.02). The associations of E/E' with higher NT-proBNP and hs-TnT persisted after multivariate adjustment for EF, LV mass and volume status.

Corresponding Author: Ruth Dubin, MD, Assistant Adjunct Professor, San Francisco VAMC, 4150 Clement St. Box 111A1, San Francisco, CA 94121, Phone: (510) 847-4955, Fax: (415) 379-5573, ruth.dubin@ucsf.edu.

Author contributions:
RFD is responsible for design, data analysis, and drafting manuscript. ALB participated in data analysis and manuscript revision; JT participated in data analysis and manuscript revision; NBS assisted in study design and analysis of echocardiograms; DA provided reads on echocardiograms; KJ assisted with design, analysis and manuscript revision.

Conflict of Interest Statement: Nelson Schiller is a consultant to Cardiocore for projects unrelated to the current manuscript. The other authors have no financial conflicts of interest to declare.

Conclusions—TDI may be more useful in evaluating cardiac function than traditional measures of diastolic dysfunction in the ESRD population.

Keywords

Doppler tissue imaging; End-stage renal disease

Introduction

Diastolic dysfunction is common in patients with end-stage renal disease (ESRD) (1-3), occurring in up to 100% of patients in one series (2). Heart failure accounts for 45% of cardiovascular events (4), and diastolic dysfunction, as measured by tissue Doppler imaging (TDI) is associated with higher mortality in the ESRD population (5-9). Despite its high prevalence and associated morbidity, diastolic heart failure in the ESRD population remains poorly understood and vastly undertreated, not only due to the absence of effective treatments, but also due to limitations of current diagnostic imaging modalities and terminology. For example, we currently lack methods to discriminate among the majority of hemodialysis patients who fall into the category of mildly impaired diastolic function. Furthermore, diastolic function can be difficult to measure accurately among patients on hemodialysis due to frequent volume shifts.

E/E' is the ratio of early blood velocity (E) to early tissue velocity (E') at the mitral annulus during left ventricular (LV) filling. E/E' is associated in a linear fashion with invasively measured LV filling pressures (7, 8); it is considered a surrogate measure of increased LV wall stress, which itself is caused by multiple factors including volume overload and ventricular stiffness. As such, higher E/E' is sometimes used as an adjunctive measure of diastolic function. NT-proBNP is a strong, independent predictor of mortality in the ESRD population (10). NT-proBNP is renally cleared, unlike BNP (11). While the association of E/E' with N-terminal brain natriuretic peptide (NT-proBNP) is established in cohorts without chronic kidney disease (12-14), this association may not hold true in ESRD. One aim of this study was to examine the relationship of E/E', as a marker of LV wall stress, with NT-proBNP in patients with ESRD; we hypothesized that categories based on E/E' would more closely correlate with NT-proBNP than would traditional categories of diastolic function (normal, impaired, pseudonormal and restrictive diastolic function). If true, this would support the utility of E/E' in ESRD patients, in whom traditional categories of diastolic dysfunction may not be reliable.

Another purpose of this study was to evaluate E/E' as a marker of myocardial injury in this population. Cardiac troponin T (cTnT) is a strong predictor of mortality among patients with end-stage renal disease (15-19); this holds true when Troponin T is measured by the high sensitivity troponin T (hs-TnT) assay, which detects troponin T in 100% of ESRD patients (10). cTnT levels are associated with left ventricular hypertrophy (LVH) (19) and macrovascular coronary disease (18). Yet, in some ESRD cohorts, severity of LVH did not correlate with cTnT levels (20); subclinical myocardial infarction was demonstrated by late gadolinium enhancement in only a minority of ESRD patients with elevated cTnT (21). Thus, structural and macrovascular heart disease appear not to be the only determinants of

troponin T in patients with ESRD. We hypothesized that ventricular stiffness, one of the contributing factors to E/E', may be associated with myocardial injury, as measured by hs-TnT, through a common causative mechanism such as microvascular disease.

Methods

Participants

We recruited and studied 40 patients on chronic hemodialysis from the San Francisco Veterans Affairs Medical Center (SFVAMC), San Francisco General Hospital, and University of California San Francisco (UCSF)-Mt. Zion Hospital between February 2010 and February 2011, and E/E' was successfully measured in 35. The original aim of this study was to measure echocardiographic changes during dialysis; patients underwent echocardiograms directly before and then during the last hour of dialysis during a dialysis session at the SFVAMC. For the current analyses, we utilized only pre-dialysis echocardiograms. To be included, patients had to be on a stable chronic hemodialysis regimen. Exclusion criteria were as follows: NYHA class III or IV heart failure, significant valvular disease, current treatment for infection, major surgery within 1 month, newly diagnosed or metastatic cancer, myocardial infarction within the last 6 months, active angina, ongoing cocaine or intravenous drug use, current chemotherapy, or cognitive deficit limiting ability to give informed consent. Among eligible participants at the three chronic hemodialysis units, thirty-five patients declined to participate, usually citing logistical issues. The protocol was approved by the UCSF Committee for Human Research and the SFVAMC Research and Development Committee, and patients gave written informed consent.

Measurements

Predictors—Echocardiograms were performed immediately before dialysis using a Siemens Sequoia Model C512 with a 3.5 MHz transducer. Date, time and patient identification were removed from echocardiograms, which were then submitted to an established reading center (Cardiocore Labs, Daly City CA) where they were read by a single blinded reader (D.A.). LV mass was measured using a truncated ellipsoid technique (22), then indexed to body surface area calculated by Mosteller formula (23). End diastolic volume and end systolic volume were measured from images obtained in apical two- and four- chamber views, and calculated according to the biplane method of discs (modified Simpson's rule) (22). E' was measured by TDI from the lateral mitral annulus. Traditional categories of diastolic function were determined by a cardiologist (A.L.B.) using primarily E to A ratio (E/A), mitral deceleration time, and pulmonary vein flow. E/E' was considered as a criterion for traditional diastolic function only if the pulmonary vein flow was equivocal or discordant with the other variables. Participants with atrial fibrillation were not classified into traditional categories of diastolic function; these three participants had missing data for diastolic category, but E/E' was measured in all three. Impaired relaxation was defined as E/A < 1.0; pseudonormalization defined as E/A >1.0 with diastolic dominant pulmonary vein flow or E/E' >10; restrictive diastolic function was defined as E/A > 1.5 with diastolic dominant pulmonary vein flow or E/E' >10 and mitral deceleration time <150 milliseconds.

Outcomes—Blood was collected immediately before dialysis for measurement of NT-proBNP and hs-TnT. Assays for NT-proBNP and hs-TnT were performed at the University of Maryland Clinical Chemistry Laboratories. The Roche NT-proBNP assay (Roche Diagnostics, Indianapolis, Indiana) has an analytical range of 5 to 35,000 pg/ml and coefficient of variation of <10% within this range. The Roche Elecsys immunoassay for cardiac troponin T has an analytical range of 3 to 10,000 ng/L and a coefficient of variation of 9% at 13.5 ng/L (the 99th percentile in a healthy reference group). (24)

Covariates—Data on demographics, comorbidities and medications were collected from the medical record. Patients with a history of myocardial infarction, coronary stenting or bypass were considered to have a history of coronary artery disease. Routine measurements of systolic and diastolic blood pressure were performed by dialysis nurses with the patient sitting, directly prior to dialysis, on the same day of the echocardiogram. We used routine monthly laboratory work processed at the patients' regular dialysis facilities for values of serum calcium, phosphorus, parathyroid hormone, albumin and Kt/V (a unitless measure of dialysis efficiency based on urea removal). Left atrial end systolic volume index (LAESVI), an important correlate of diastolic dysfunction (25), was calculated as LAESV(ml)/body surface area (m^2). Mitral annular calcification, which affects tissue Doppler measurements, was graded as 0 for none, 1 for isolated lesion, 2 for patchy calcification, and 3 for contiguous (>40% of region.)

Reproducibility of TDI Measurements—In the original study protocol, patients had echocardiograms on 2 different days. In 15 patients who had repeat studies prior to dialysis <= 7 days apart, interobserver coefficient of variation for E/E' was 14%. In 15 studies examined in a blinded fashion by the reader D.A., intraobserver coefficient of variation for E/E' was 4.4%.

Statistical Analysis

We described patient characteristics in those above and below the median value of E/E'. Next, we evaluated univariate associations of continuous echocardiogram parameters (E', E/E', ejection fraction (EF) and LV mass index) and of potential covariates with NT-proBNP and hs-TnT by spearman correlation. We chose to perform analyses for both E/E' and E' alone; we were interested in whether the TDI component (E') was the driving factor behind the strong associations of E/E' (the most commonly used clinical TDI parameter) with NT-proBNP and hs-TnT. In addition, categories of E/E', diastolic dysfunction, and EF were compared by log(NT-proBNP) and log(hs-TnT). We performed multivariate regression of each biomarker on tertile of E/E' and E' alone by adjusting for covariates associated with NT-proBNP, hs-TnT or E/E' at a significance of ≤0.2. Due to the modest sample size, we chose *a priori* to use a less restrictive p value to select covariates for multivariate analysis and we limited models to five covariates.

Model 1 included demographics, comorbidities and laboratory variables (gender, months on dialysis, renal disease attributed to diabetes or hypertension, calcium, hemoglobin). Model 2 included echocardiographic factors (EF and LV mass index). Model 3 included hemodynamics and volume status (diastolic blood pressure, weight gain since last dialysis,

inferior vena cava (IVC) diameter). In Model 4, we adjusted for NT-proBNP in the association of TDI parameters with hs-TnT; we adjusted for hs-TnT in the association of TDI parameters with NT-proBNP. Regression analyses were back-transformed to yield an estimate for fold increase of biomarker per tertile of E/E' or E'. All analyses were performed using STATA 11 (StataCorp, College Station, TX, USA).

Results

The mean (SD) age of our study cohort was 63(±14) years, the median dialysis vintage was 3 years, and 7(20%) were women. Diabetes was present in 17(49%) of our participants, history of coronary artery disease (myocardial infarction, coronary stent, coronary artery bypass graft) in 7(20%). Median (IQR) for E/E' was 6.7 (6.0-9.6). The majority had normal or mildly impaired diastolic function, and only three had ejection fraction <50%. (Table I) Atrial fibrillation was present in 3 subjects, (9%) and the rest were in normal sinus rhythm.

E/E' had strong univariate associations with NT-proBNP and hs-TnT. Considered alone, E and E' differed in their associations with these biomarkers. Defining statistical significance as $p \leq 0.2$, higher E was associated with higher NT-proBNP, but not with hs-TnT. Lower E' was associated with higher hs-TnT and NT-proBNP. We evaluated several indicators of volume status and found a number of significant associations: diastolic blood pressure correlated with hs-TnT, weight gain since last dialysis correlated with E/E' and E', and IVC expiratory diameter correlated with NT-proBNP. LAESVI was significantly correlated with E/E', E' and both biomarkers. (Table II) Compared to no MAC, MAC graded as contiguous (grade 3, >40% of region) was associated with a 5 unit higher E/E' ($p=0.005$), but grades 1 and 2 MAC were not associated with higher E/E'. Covariates that were not associated with either biomarker or TDI included the following parameters: age, history of myocardial infarction, diabetes, 'current weight-dry weight,' systolic blood pressure, caval index, phosphorus or Kt/V (Table 1). Higher tertiles of E/E' were associated with higher NT-proBNP and higher hs-TnT. Surprisingly, worse traditional categories of diastolic function were associated with lower hs-TnT, and EF was associated with neither biomarker. (Figure I)

Participants in the second tertile of E/E' had 3-fold higher levels of NT-proBNP ($p=0.07$), and those in the third tertile had 6-fold higher levels of NT-proBNP ($p=0.003$). These associations were mildly attenuated by multivariate adjustment. (Table III) In contrast, E' alone did not have statistically significant associations with NT-proBNP. Participants in the highest tertiles of E/E' and E' alone had higher levels of hs-TnT, and these associations were independent of NT-proBNP. (Tables III and IV) To test whether high grade MAC affected these results, we analyzed unadjusted models for E/E' and E' excluding three participants with Grade 3 MAC, and the results were not substantially different.

Discussion

In this study of hemodialysis patients, we report the novel finding that TDI (both higher E/E' and lower E') are associated with higher hs-TnT independently of EF, LV mass and

volume status. While higher E/E' was strongly associated with higher NT-proBNP and hs-TnT, EF and traditional categories of diastolic function were not.

It is notable that E/E' was associated with myocardial injury, independent of LV mass index and volume status indicators. Several factors likely contribute to patients' measured E/E', including volume status and ventricular stiffness. Ventricular stiffness is a consequence of diverse molecular and cellular processes. Biopsy studies from patients with heart failure and preserved EF show a reduced fraction of elastic type titin, the sarcomeric protein that acts as an elastic band to modulate myocyte stiffness. Microvascular endothelial dysfunction potentiates cellular hypertrophy and stiffening by decreasing the availability of nitric oxide for cardiomyocytes. Collagen deposition is upregulated, and fibrosis leads to a stiffer ventricle (26). These processes do not always coincide with hypertrophy of total ventricular mass. While hypertrophy is often a characteristic of diastolic dysfunction, diastolic dysfunction may occur in the absence of hypertrophy. For example, in the Valsartan In Diastolic Dysfunction trial only 3% of patients with diastolic dysfunction had hypertrophy(27). It is possible that a common pathology, such as microvascular disease, causes both ventricular stiffness and ischemic troponin leak, and this unmeasured phenomenon underlies the association of E/E' with hs-TnT.

Higher E/E', a surrogate measure of LV filling pressures, is associated with higher mortality in ESRD patients (5, 6, 9), and NT-proBNP independently predicts mortality in this population (10). NT-proBNP is widely accepted as a biomarker of volume status and heart failure in populations without chronic kidney disease (12-14). However, since it is cleared by the kidneys (unlike BNP) (11), it is not known whether it correlates with any parameter of cardiac function *per se* in chronic kidney disease populations or if it is largely a marker of renal function. In this cohort of patients on hemodialysis, we found that E/E' strongly correlates with higher NT-proBNP. Remarkably, worsened traditional diastolic categories were not associated with higher NT-proBNP and were associated with *lower* hs-TnT. These findings suggest that TDI may be a useful marker of cardiac function in this population.

There are several limitations to our pilot study. The modest number of patients precluded extensive multivariate regression and increases the chance of type II error. Thus, we cannot rule out associations that did not reach statistical significance among these participants and cannot account for unmeasured confounders. In addition, we could not stratify analyses on ejection fraction, since only three participants had ejection fraction <50%. TDI was measured at the lateral annulus rather than averaging TDI from septal and lateral aspects of the annulus. Although the utility of lateral annulus TDI in persons with normal ejection fraction is supported by the literature (28, 29), it should be noted that our values for E/e' would likely be lower than if they were averaged with septal TDI. Three participants with atrial fibrillation could not be categorized by traditional diastolic categories, and this may have influenced the association between traditional category and biomarker. The influence of volume status on diastolic function represents an inherent conundrum for researchers of diastolic function in patients with chronic kidney disease, who are often hypervolemic. We lack a gold standard to assess volume status; while our estimates of volume status are commonly used in clinical practice, weights and IVC diameter are influenced by a number of factors that cannot be controlled for, such as scale calibration and image quality. In

addition, our studies were performed prior to a dialysis session, when volume status is not optimized. Larger studies in which dialysis patients are studied on the day after dialysis could address these limitations.

Nevertheless, this study demonstrates that TDI, systematically measured in hemodialysis patients at a standard time in relation to dialysis and interpreted by a single blinded reader, has strong, independent associations with both NT-proBNP and hs-TnT. Further research may be warranted to identify a link between E/E' and hs-TnT, such as microvascular disease, that may contribute to both ventricular stiffness and ischemia. TDI may be more useful in evaluating cardiac function than traditional measures of systolic and diastolic dysfunction in this population.

Acknowledgments

Funding: Funding for this project came from the following sources. 1. Individual Investigator Grant, University of California San Francisco Academic Senate, San Francisco, CA 2. Grant Huntington Fund provided by the Research Evaluation and Allocation Committee in the University of California San Francisco, School of Medicine Dean's Office, San Francisco, CA. 3. National Institute of Diabetes and Digestive and Kidney Diseases, 1K24-DK085153-02 4. National Institute of Diabetes and Digestive and Kidney Diseases, 1K23-DK092354-01A1 5. UCSF Clinical and Translational Science Institute Grant Number UL1 TR000004 4. Roche Diagnostics Corporation (Indianapolis, Indiana) supplied reagents for the NT-proBNP and hs-TnT assays, but did not provide study funding.

References

1. Fathi R, Isbel N, Haluska B, et al. Correlates of subclinical left ventricular dysfunction in ESRD. Am J of Kidney Dis. 2003; 41:1016–25. [PubMed: 12722036]
2. Su CT, Liu YW, Lin JW, et al. Increased procollagen type I C-terminal peptide levels indicate diastolic dysfunction in end-stage renal disease patients undergoing maintenance dialysis therapy. J Am Soc of Echocardiogr. 2012; 25:895–901. [PubMed: 22658561]
3. Kimura H, Takeda K, Tsuruya K, et al. Left ventricular mass index is an independent determinant of diastolic dysfunction in patients on chronic hemodialysis: a tissue Doppler imaging study. Nephron Clin Pract. 2011; 117:c67–73. [PubMed: 20689327]
4. USRDS. 2012 Atlas of CKD & ESRD. 2012; 2(Ch. 4) Available from: http://www.usrds.org/2012/pdf/v2_ch4_12.pdf.
5. Dogan U, Ozdemir K, Akilli H, et al. Evaluation of echocardiographic indices for the prediction of major adverse events during long-term follow-up in chronic hemodialysis patients with normal left ventricular ejection fraction. Eur Rev Med Pharmacol Sci. 2012; 16:316–24. [PubMed: 22530347]
6. Iwabuchi Y, Ogawa T, Inoue T, et al. Elevated E/E' predicts cardiovascular events in hemodialysis patients with preserved systolic function. Intern Med. 2012; 51:155–60. [PubMed: 22246482]
7. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009; 10:165–93. [PubMed: 19270053]
8. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation. 2000; 102:1788–94. [PubMed: 11023933]
9. Wang AY, Wang M, Lam CW, et al. Left ventricular filling pressure by Doppler echocardiography in patients with end-stage renal disease. Hypertension. 2008; 52:107–14. [PubMed: 18474835]
10. McGill D, Talaulikar G, Potter JM, et al. Over time, high-sensitivity TnT replaces NT-proBNP as the most powerful predictor of death in patients with dialysis-dependent chronic renal failure. Clin Chimica Acta. 2010; 411:936–9.
11. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. Eur J Heart Fail. 2004; 6:261–8. [PubMed: 14987574]

12. McGrady M, Reid CM, Shiel L, et al. N-terminal B-type natriuretic peptide and the association with left ventricular diastolic function in a population at high risk of incident heart failure: results of the SCReening Evaluationof the Evolution of New-Heart Failure Study (SCREEN-HF). Eur J Heart Fail. 2013; 15:573–80. [PubMed: 23338855]
13. Sonoda H, Ohte N, Goto T, et al. Plasma N-terminal pro-brain natriuretic peptide levels identifying left ventricular diastolic dysfunction in patients with preserved ejection fraction. Circ J. 2012; 76:2599–605. [PubMed: 22878353]
14. Grewal J, McKelvie R, Lonn E, et al. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. Eur J of Heart Fail. 2008; 10:252–9. [PubMed: 18331967]
15. Apple FS, Murakami MM, Pearce LA, et al. Multi-biomarker risk stratification of N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and cardiac troponin T and I in end-stage renal disease for all-cause death. Clin Chem. 2004; 50:2279–85. [PubMed: 15364888]
16. Hallen J, Madsen L, Ladefoged S, et al. Incremental value of a combination of cardiac troponin T, N-terminal pro-brain natriuretic peptide and C-reactive protein for prediction of mortality in end-stage renal disease. Scand J Urol Nephrol. 2011; 45:151–8. [PubMed: 21091090]
17. Khan NA, Hemmelgarn BR, Tonelli M, et al. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. Circulation. 2005; 112:3088–96. [PubMed: 16286604]
18. Sharma R, Gaze DC, Pellerin D, et al. Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T. Heart. 2006; 92:804–9. [PubMed: 16216854]
19. Mallamaci F, Zoccali C, Parlongo S, et al. Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis. 2002; 40:68–75. [PubMed: 12087563]
20. deFilippi C, Wasserman S, Rosanio S, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. JAMA. 2003; 290:353–9. [PubMed: 12865376]
21. deFilippi CR, Thorn EM, Aggarwal M, et al. Frequency and cause of cardiac troponin T elevation in chronic hemodialysis patients from study of cardiovascular magnetic resonance. American J of Cardiol. 2007; 100:885–9.
22. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc of Echocardiogr. 2005; 18:1440–63. [PubMed: 16376782]
23. Verbraecken J, Van de Heyning P, De Backer W, et al. Body surface area in normal-weight, overweight, and obese adults. A comparison study. Metabolism. 2006; 55:515–24. [PubMed: 16546483]
24. Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem. 2010; 56:254–61. [PubMed: 19959623]
25. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc of Echocardiogr. 2009; 10:165–93.
26. Paulus WJ, Tschope C. A Novel Paradigm for Heart Failure with Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. J Am Coll Cardiol. 2013; 62:263–71. [PubMed: 23684677]
27. Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet. 2007; 369:2079–87. [PubMed: 17586303]
28. Rivas-Gotz C, Manolios M, Thohan V, et al. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. Am J Cardiol. 2003; 91:780–4. [PubMed: 12633827]
29. Kasner M, Westermann D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection

fraction: a comparative Doppler-conductance catheterization study. Circulation. 2007; 116:637–47. [PubMed: 17646587]

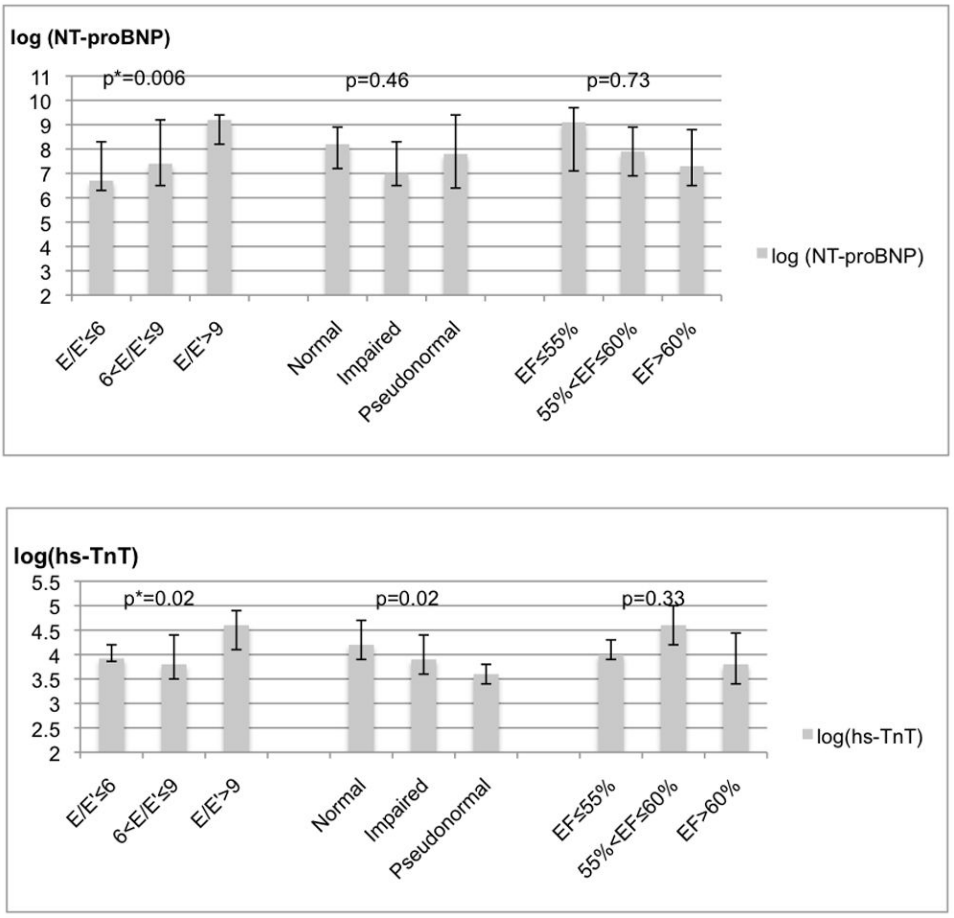

Figure I.

a, b. Comparison of Log(hs-TnT) and Log(NT-proBNP) Across Categories of E/E', Diastolic Function Category and Ejection Fraction

Higher tertiles of E/E' were associated with higher NT-proBNP and hs-TnT with $p<0.05$. Categories or worse diastolic function were not significantly associated with NT-proBNP, but were associated with lower hs-TnT. Categories of lower ejection fraction did not have statistically significant associations with either biomarker. *p for trend.

Table I

Characteristics of Study Participants, N=35

		All patients	E/E' < 7 N=18	E/E' ≥ 7 N=17	p*
Age (years)		63 (±14)	63 (±14)	63 (±14)	0.88
Months on dialysis		40 (14, 65)	26 (12,55)	45 (16, 80)	0.21
Women		7 (20%)	2 (11%)	5 (29%)	0.18
History of diabetes mellitus		17(49%)	8(44%)	9(53%)	0.62
ESRD attributed to hypertension or diabetes		23(66%)	10(55%)	13(76%)	0.19
History of coronary artery disease †		7(20%)	4(22%)	3(18%)	0.74
ACE-I or ARB ‡		14(40%)	10(56%)	4(24%)	0.05
Beta blocker		26(74%)	15(83%)	11(65%)	0.21
Statin		17(49%)	9(50%)	8(47%)	0.86
Epogen (units per week)		6000 (60, 9000)	5500 (500, 8000)	6000 (60, 15000)	0.41
Systolic blood pressure (mmHg)		144 (±24)	142 (±24)	145 (±23)	0.53
Diastolic blood pressure (mmHg)		75 (±12)	75 (±12)	75 (±13)	0.80
Current weight – dry weight (kg)		2.3(1.6, 3.3)	2.1(1.4, 3.2)	2.7(1.8, 3.3)	0.12
Weight gain since last dialysis (kg)		2.0(1.5, 3)	1.8(1.4, 2.2)	2.4(1.7, 3)	0.20
Calcium (mg/dL)		8.8 (±0.77)	8.9 (±0.67)	8.6 (±0.86)	0.19
Phosphorus (mg/dL)		4.9 (4.0,6.3)	5.2 (4.2, 6.5)	4.7 (3.9, 5.5)	0.28
Parathyroid hormone (mg/dL)		287 (210, 410)	310 (180, 390)	290 (220, 410)	0.77
Hemoglobin (g/dL)		11 (±1.2)	11.4 (±0.94)	11 (±1.4)	0.15
Kt/v §		1.6 (±0.3)	1.6 (±0.3)	1.6 (0.4)	0.66
Left ventricular mass index (g/m^2)		94 (81, 120)	86 (81, 114)	103(87, 120)	0.28
IVC expiratory diameter (cm)		1.4(±0.34)	1.4(±0.3)	1.5(±0.33)	0.20
IVC index (%) ‖		42(36, 53)	48(33, 53)	40(38, 47)	0.80
Mitral annular calcification	None	7 (21%)	4 (22%)	3 (19%)	0.59
	Isolated	18 (53%)	11 (61%)	7 (44%)	
	Patchy	6 (18%)	2 (11%)	4 (25%)	
	Contiguous (>40%)	3 (9%)	1 (6%)	2 (13%)	
LAESVI (ml/m^2) #		27 (±9.7)	23 (±6.3)	33 (±10)	0.001

		All patients	E/E' < 7 N=18	E/E' ≥ 7 N=17	p*
LV ** ejection fraction (%)		58 (±6.9)	57 (±7.7)	60 (±5.9)	0.45
LV diastolic function	Normal	11(37%)	4(24%)	7(54%)	0.21
	Impaired	14(47%)	10(59%)	4(31%)	
	Pseudonormal	5(17%)	3(18%)	2(16%)	
E (cm/s)		97 (±26)	82 (±15)	114 (±25)	0.001
E' (cm/s)		13 (±3.2)	14 (±3.4)	11(±3.4)	0.01
E/E'		6.7 (6.0, 9.6)	6.0(5.4, 6.2)	9.6 (9.0, 10.2)	0.0001

*N(%), Mean (±SD), Median (IQR); kruskal–wallis for continuous predictors, chi^2 for dichotomous predictors

†defined as history of myocardial infarction, coronary stenting or coronary artery bypass graft

‡angiotensin converting enzyme inhibitor or angiotensin receptor blocker

§K=urea clearance t=time on dialysis V=volume of distribution. Kt/V is a measure of dialysis adequacy

//IVC index = {((expiratory IVC diameter)-(inspiratory IVC diameter))/(expiratory IVC diameter)} × 100%

#left atrial end-systolic volume index

**left ventricular

Table II

Spearman's Correlations of Volume Status Markers, Continuous Echo Parameters, NT-proBNP and hs-TnT

	NT-proBNP (pg/ml)		hs-TnT (pg/ml)		E' (cm/s)		E/E'	
	Rho	*p*	*Rho*	p	*Rho*	p	*Rho*	p
Systolic blood pressure (mmHg)	0.12	0.49	-0.17	0.31	0.13	0.47	0.006	0.97
Diastolic blood pressure (mmHg)	0.05	0.80	-0.34	0.05	-0.09	0.62	-0.005	0.98
Weight gain since last dialysis (kg)	0.08	0.66	-0.16	0.37	-0.39	0.02	0.31	0.07
LAESVI (ml/m^2)	0.59	<0.001	0.38	0.03	-0.42	0.01	0.58	<0.001
LV mass index (g/m^2)	0.43	0.01	0.17	0.32	-0.03	0.86	0.04	0.82
IVC expiratory diameter (cm)	0.31	0.10	0.18	0.35	0.19	0.31	0.03	0.89
Ejection fraction (%)	-0.2	0.40	-0.24	0.16	-0.06	0.71	0.09	0.60
E (cm/s)	0.42	0.01	0.20	0.25	--	--	--	--
E' (cm/s)	-0.26	0.14	-0.3	0.07	--	--	--	--
E/E'	0.48	0.004	0.37	0.03	--	--	--	--

Table III

Associations of E/E' Tertiles with Concentrations of NT-proBNP and hs-TnT Expressed as Fold Increase Over Tertile I

NT-proBNP	Unadjusted		Model 1		Model 2		Model 3		Model 4	
Tertile E/E'	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**
I (E/E'≤6)	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--
II (6<E/E'≤9)	2.7 (0.92, 7.9)	0.07	2.6 (0.86, 7.8)	0.09	2.3 (0.81, 6.5)	0.12	2.3 (0.72, 7.5)	0.15	2.5 (0.86, 7.5)	0.09
III (E/E'>9)	5.9 (1.9, 18.4)	0.003	9.0 (2.4, 34)	0.002	5.4 (1.9, 16)	0.003	4.9 (1.4, 20)	0.02	4.0 (1.1, 14)	0.03
hs-TnT										
I (E/E'≤6)	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--
II (6<E/E'≤9)	1.09 (0.66, 1.9)	0.71	1.02 (0.56, 1.9)	0.95	1.1 (0.65, 1.9)	0.73	1.1 (0.65, 1.7)	0.84	1.02 (0.63, 1.7)	0.92
III (E/E'>9)	1.92 (1.14, 3.2)	0.016	1.77 (0.89, 3.5)	0.10	1.9 (1.1, 3.2)	0.02	2.1 (1.2, 3.5)	0.009	1.8 (1.0, 3.0)	0.03

Model 1 adjusted for gender, months on dialysis, renal disease attributed to diabetes or hypertension, calcium, hemoglobin
Model 2 adjusted for ejection fraction, left ventricular mass index
Model 3 adjusted for diastolic blood pressure, weight gain since last dialysis and IVC exp diameter
Model 4 adjusted for hs-TnT in model for outcome NT-proBNP, adjusted for NT-proBNP in model for outcome hs-TnT

Table IV

Associations of E' Tertiles with Concentrations of NT-proBNP and hs-TnT Expressed as Fold Increase Over Tertile I

NT-proBNP	Unadjusted		Model 1		Model 2		Model 3		Model 4	
Tertile E'	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**	**Fold Increase (95% CI)**	**p**
I (14-22)	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--
II (10.7-13.9)	1.5 (0.44, 5.3)	0.5	1.8 (0.6, 6.1)	0.35	1.4 (0.38, 5.3)	0.63	1.2 (0.29, 5.3)	0.78	1.5 (0.5, 4.9)	0.46
III (7.4-10.5)	2.0 (0.57, 7.0)	0.3	2.5 (0.6, 9.8)	0.18	2.0 (0.63, 6.5)	0.23	1.6 (0.41, 6.5	0.50	0.97 (0.25, 3.7)	0.96
hs-TnT										
I (14-22)	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--	*(ref)*	--
II (10.7-13.9)	1.0 (0.57, 1.6)	0.9	1.0 (0.54, 1.7)	0.89	1.0 (0.57, 1.9)	0.9	1.02 (0.57, 1.8)	0.94	0.86 (0.53, 1.4)	0.52
III (7.4-10.5)	1.7 (1.0, 2.8)	0.04	1.6 (0.88, 3.0)	0.11	1.8 (1.0, 3.0)	0.04	1.6 (0.96, 2.8)	0.07	1.7 (1.1, 2.8)	0.03

Model 1 adjusted for gender, months on dialysis, renal disease attributed to diabetes or hypertension, calcium, hemoglobin
Model 2 adjusted for ejection fraction, left ventricular mass index
Model 3 adjusted for diastolic blood pressure, weight gain since last dialysis and ivc exp diameter
Model 4 adjusted for hs-TnT in model for outcome NT-proBNP, adjusted for NT-proBNP in model for outcome hs-TnT