Left ventricular growth after 1 year of haemodialysis does not correlate with arteriovenous access flow: a prospective cohort study

Swapnil Hiremath¹, Steve P. Doucette², Robert Richardson³, Kwan Chan⁴, Kevin Burns¹ and Deborah Zimmerman¹

¹Division of Nephrology, Kidney Research Centre, Ottawa Health Research Institute, Ottawa, Ontario, Canada, ²Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario, Canada, ³University Health Network, Toronto, Canada and ⁴University of Ottawa Heart Institute, Ottawa, Canada

Correspondence and offprint requests to: Deborah Zimmerman; E-mail: dzimmerman@ottawahospital.on.ca

Abstract

Background. The incidence of congestive heart failure is 3-fold greater than that of acute coronary syndrome in haemodialysis (HD) patients. The purpose of this study was to determine if blood flow through an arteriovenous (AV) access contributes to an increase in left ventricular mass (LVM) that may increase the risk of congestive heart failure.

References


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Methods. We conducted a 1-year prospective cohort study at two Canadian centres of HD patients at high risk for congestive heart failure who had a first AV access created. Patients underwent echocardiography and measurement of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels before and 1-year post-AV access creation. Access flows were measured within the first month of access maturation and 1-year post-access creation. Data were analysed using descriptive statistics, Student's t-test, correlation coefficients and regression.

Results. One-year post-AV access creation, LVM increased by 12.2 ± 32% (P = 0.025) and plasma NT-proBNP levels increased by 170 ± 465% (P = 0.02). The average AV access blood flow did not correlate with an increase in LVM or NT-proBNP levels.

Conclusions. In patients on chronic HD after 1 year, AV access flow does not correlate with increases in LVM by echocardiography or plasma levels of NT-proBNP.

Keywords: arteriovenous access; haemodialysis; left ventricular mass; NT-proBNP

Introduction

Cardiovascular disease accounts for the majority of deaths in haemodialysis (HD) patients, with an age-adjusted relative risk approximately 20 times greater than the general population [1]. The incidence of heart failure is almost three times greater than the incidence of acute coronary syndrome in HD patients and both cardiovascular diagnoses are equally lethal with a 3-year mortality rate of approximately 80% [2–4]. Traditional as well as non-traditional factors likely contribute to this increased risk in HD patients [5]. In one study, the independent risk factors for de novo cardiac failure in HD patients were increasing age, diabetes mellitus (DM), systolic dysfunction, worsening anaemia, lower albumin and increasing diastolic blood pressure (DBP) [6]. Left ventricular hypertrophy (LVH) with normal systolic function and LVH secondary to LV dilatation (eccentric LVH) have also been associated with an increased risk of de novo cardiac failure and death in patients with end-stage renal disease [1]. However, the risk of de novo heart failure was substantially higher in patients treated with HD compared to those treated with peritoneal dialysis (PD) [7]. Although there are several treatment differences between HD and PD, the presence of an arteriovenous (AV) access in HD may account for the enhanced risk of de novo heart failure.

Arteriovenous fistulae (AVF) are recommended as the accesses of choice for HD patients based on their clear superiority over central venous catheters (CVC) in terms of infections, thrombosis rates and urea clearance [8–10]. However, there are important haemodynamic consequences linked to the creation of an AVF including an instantaneous increase in cardiac output and a fall in peripheral vascular resistance [11–13]. Importantly, several cases of high-output cardiac failure associated with AVF in HD patients have been reported [14,15]. In a study of 12 pre-dialysis patients, left ventricular mass (LVM) index increased by 5.1 g/m².7 ± 0.03 at 1 month and 8.7 g/m².7 at 3 months post-AVF creation [16]. Regression of LVH has also been documented in kidney transplant recipients after AVF ligation [17]. Lastly, AVF creation has been associated with an increase in natriuretic peptides in a short-term study of 16 chronic renal failure patients [18]. Despite this indirect evidence suggesting a link between left ventricular remodelling and AVF creation, there have been no long-term prospective studies evaluating the effect of AV access flow on LVM.

Materials and methods

We conducted a 1-year prospective cohort study at two Canadian HD centres to examine the effect of the creation of a first AVF/arteriovenous graft (AVG) in HD patients considered at increased risk to develop congestive heart failure. Our objectives were 2-fold: (i) to determine if flow through an AVF/AVG for HD correlated with an increase in LVM and (ii) to determine if plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) increased after the creation of an AVF/AVG.

Study design

The study was conducted in accordance with the Helsinki Declaration and received research ethics board approval at both Canadian institutions involved in patient enrolment. HD patients and chronic kidney disease patients who were expected to start HD within 6 months were screened for inclusion and exclusion criteria. The inclusion criteria consisted of (i) an increased risk to develop heart failure (age >50 or DM), (ii) a first AVF/AVG to be created, (iii) technically adequate cardiac studies (for the primary objective) and (iv) stable haemoglobin (>100 g/L). Patients were not invited to participate if (i) expected survival was <1 year, (ii) they were expected to receive a living donor kidney transplant within 1 year, (iii) they plan to transfer to an alternate treatment modality within 1 year, such as home HD or PD or (iv) if there was a reasonable possibility of recovery of renal function.

Data collection

Demographic data (age, cause of end-stage renal disease, gender, number and categories of comorbidities) were recorded at study entry. The usual monthly blood work (haemoglobin, serum levels of albumin, calcium and phosphate) was collected. The haemoglobin target was 11.0–12.0 g/L, maintained with the use of intravenous iron and erythropoietin. Target serum calcium concentration was within the normal range and phosphate <5.6 mg/dL was maintained with the use of calcium carbonate, calcitriol and dietician intervention. Systolic blood pressure (SBP) and DBP post-HD were recorded mid-week on the day of monthly blood work and the average value calculated over the 1 year of follow-up. Blood pressure was maintained at <140/90 mmHg post-dialysis through adjustment of antihypertensive medications and dry weight as required. Similarly, inter-dialytic weight gain was assessed on the day of monthly blood work and averaged over the 1 year of follow-up.

Echocardiograms

Each patient underwent M-mode echocardiography approximately 2 to 3 weeks prior to access creation and again at 12 months post-access creation. Echocardiograms were performed mid-week at the completion of HD when the patients were at their clinically estimated dry weight. All echocardiograms were stored on videocassettes and read by a single cardiologist who was blinded to the access type/location, access surgical date and amount of blood flow through the access. The echocardiographic dimensions were measured following the American Society of Echocardiography guidelines [19]. As the longitudinal comparison is within patients
and not between patients, LVM not indexed to body surface area was calculated according to the following formula [20]:

\[
\text{LVmass (in grams)} = 0.8 \times 1.04 \times \left[ (LVIDD + IVS + PW)^3 - (LVIDD)^3 \right] + 0.6
\]

**Access flow**

Flow through the AVF/AVG was measured using the Krivitski ultrasound dilution method [21]. Access blood flow was determined as the average of two separate measurements taken 5 to 10 min apart during the first 30 min of the same dialysis session. Access flow measurements were taken within the first month of access maturation and use and 12 months post-access creation.

**Measurement of plasma NT-proBNP levels**

Plasma levels of NT-proBNP were measured before access creation and repeated at 12 months post-surgery. Blood samples were drawn midweek pre-dialysis after 20 to 30 min of resting in a semi-recumbent position. Samples were collected in cooled ethylenediaminetetraacetic acid-containing vacutainer tubes, placed on ice and centrifuged within 30 min at \(-4^\circ\text{C}\). The plasma was stored at \(-80^\circ\text{C}\) for later analysis using a commercially available electrochemiluminescence assay kit (Elecsys ProBNP—Roche, Mannheim, Germany).

**Analysis**

Summary descriptive statistics are presented for the collected baseline data, access flow and time-averaged variables of blood pressure, serum levels of calcium, phosphate, haemoglobin and albumin. Where indicated, data are presented as the mean ± SD or median and interquartile range. Student’s paired \(t\)-test was used to determine if the LVM (mean delta) changed over time for patients with two technically adequate echocardiograms. To account for differences in baseline values, we report the percentage delta change in LVM. A post hoc analysis was repeated with LVM index (LVMi). Pearson’s correlation coefficients were then used to test for the association between the variables, mean access flow (average of the flow at access maturation and at 1-year post-creation), initial access flow and percent change in LVM. A similar analysis, with the exception that Spearman’s rho correlation coefficients were calculated, was undertaken for plasma NT-proBNP concentration using the percentage change to account for differences in baseline values. Lastly, we undertook a multiple regression analysis with LVMi as the dependent variable and access flow, initial access flow and percent change in LVM as independent variables.

**Table 1. Baseline and 1-year average characteristics of the 47 patients who completed the study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>One-year mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years [mean ± SD]</td>
<td>59.1 ± 14.9</td>
<td></td>
</tr>
<tr>
<td>Gender, male [n (%)]</td>
<td>30 (64.8)</td>
<td></td>
</tr>
<tr>
<td>DM [n (%)]</td>
<td>23 (48.9)</td>
<td></td>
</tr>
<tr>
<td>Access type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVF [n (%)]</td>
<td>44 (93.6)</td>
<td></td>
</tr>
<tr>
<td>AVG [n (%)]</td>
<td>3 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity score</td>
<td>5.96 (3.2)</td>
<td>136(12)/73 (9)</td>
</tr>
<tr>
<td>SBP/DBP, mmHg [mean ± SD]</td>
<td>137(25)/76(12)</td>
<td>136(12)/73 (9)</td>
</tr>
<tr>
<td>Haemoglobin, g/dL [mean ± SD]</td>
<td>11.9 (1.1)</td>
<td>11.8 (0.8)</td>
</tr>
<tr>
<td>Calcium, mg/dL [mean ± SD]</td>
<td>9.24 (0.64)</td>
<td>9.24 (0.44)</td>
</tr>
<tr>
<td>Phosphate, mg/dL [mean ± SD]</td>
<td>4.81 (1.31)</td>
<td>4.84 (0.88)</td>
</tr>
<tr>
<td>Albumin, g/dL [mean ± SD]</td>
<td>3.6 (0.5)</td>
<td>3.7 (0.3)</td>
</tr>
<tr>
<td>Inter-dialytic weight gain (L)</td>
<td>2.0 (1.1)</td>
<td>2.21 (0.78)</td>
</tr>
<tr>
<td>Blood flow, mL/min [mean ± SD]</td>
<td>975.4 ± 574.0</td>
<td>1071.0 ± 683.7</td>
</tr>
<tr>
<td>LVM, g [mean ± SD], (n = 38)</td>
<td>185.5 ± 82</td>
<td>192.2 ± 63</td>
</tr>
<tr>
<td>BNP, pmol/L [mean ± SD], (n = 42)</td>
<td>545.2 ± 972.7</td>
<td>808.5 ± 1227.6</td>
</tr>
</tbody>
</table>

To convert to SI units: haemoglobin (in grams per litre) multiply by a factor of 10, calcium (in millimoles per litre) multiply by 0.25, phosphate (in millimoles per litre) multiply by 0.32, albumin (in grams per litre) multiply by 10.
ession analysis to identify any predictors of an increase in LVM. The following predictor values were examined: age, diabetes, dialysis vintage, SBP, DBP, haemoglobin, albumin and reduced ejection fraction as these have been shown to be important in other studies. Additionally, we inserted average blood flow through the access and use of an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) into the model. For the purpose of the correlation and regression analyses, the baseline laboratory values have been used. The LVM and NT-proBNP analyses are limited to patients with both echocardiograms and both NT-proBNP measurements, respectively.

Results

At the two hospitals, 536 patients were screened for inclusion/exclusion criteria, of which 237 patients were eligible for the study. Eighty-six patients consented to participate (Figure 1). Of these, 17 patients were later excluded for various reasons (see Figure 1) leaving 69 participants at study entry. A further 22 patients did not complete the 1 year of follow-up due to failed AV access creation (n = 14), death (n = 7) or loss to follow-up (n = 1). The causes of death were sudden death (n = 4) and withdrawal from dialysis [n = 3, post-intracerebral bleed (1), post-myocardial infarction (1), post-gastrointestinal surgery for ischaemic bowel (1)].

The demographic and laboratory data collected on the 47 patients who completed the study are depicted in Table 1. Of the 47 patients who completed the study, 38 participants had both echocardiograms, 42 participants had both NT-proBNP measurements and 38 participants had their access flow measured twice. Twenty-nine patients had both echocardiograms and access flow measurements; 36 participants had both NT-proBNP and access flow measurements. Seven of the patients had their access created prior to starting dialysis, 10 patients had their access created while on PD and the remainder of the patients had started HD with a CVC. Ten percent of the patients had a reduced ejection fraction and 20% had a prior history of congestive heart failure. Importantly, 45% of the patients were treated with either an angiotensin-converting inhibitor (ACEI) or an angiotensin receptor blocker (ARB). The surgically created accesses included 44 AVF (22 radiocephalic, 18 basilic vein transposition, 3 brachiobasilic and 1 not documented) and 3 AVG (all forearm loop) with a mean flow of 975.4 ± 574.0 mL/min determined within 1 month of maturation (162 ± 116 days post-creation). The mean AV access flow was unchanged at 1-year post-surgical creation (1071.0 ± 683.7 ml/min, P = 0.2).

Table 2. Change in LVM and BNP; correlation with selected variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% Change in LVM (n = 29) (12.2 ± 32), correlation coefficient (P-value)¹</th>
<th>% Change in BNP (n = 36) (median, 29.2; IQR, −28.0 to 105.3), correlation coefficient (P-value)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.02 (0.89)</td>
<td>0.23 (0.14)</td>
</tr>
<tr>
<td>Charlson score</td>
<td>−0.04 (0.82)</td>
<td>0.08 (0.60)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>−0.12 (0.09)</td>
<td>0.05 (0.76)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>−0.05 (0.78)</td>
<td>0.08 (0.62)</td>
</tr>
<tr>
<td>Hgb (g/L)</td>
<td>−0.15 (0.36)</td>
<td>0.06 (0.72)</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.16 (0.35)</td>
<td>0.02 (0.91)</td>
</tr>
<tr>
<td>Reduced ejection fraction</td>
<td>0.17 (0.30)</td>
<td>0.07 (0.66)</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td>0.21 (0.22)</td>
<td>0.21 (0.18)</td>
</tr>
<tr>
<td>Initial access flow (mL/min)</td>
<td>−0.03 (0.86)</td>
<td>0.15 (0.36)</td>
</tr>
<tr>
<td>Mean access flow (mL/min)</td>
<td>−0.10 (0.56)</td>
<td>0.09 (0.60)</td>
</tr>
</tbody>
</table>

¹Using Pearson's correlation.
²Using Spearman's correlation.
Echocardiograms

Of the 47 patients who completed the study, 9 ultimately did not have paired echocardiograms that were technically adequate. For the 38 patients with two echocardiograms, the LVM increased by 6.7 ± 66.9 g (12.2 ± 32%, P = 0.025). Similarly, the LVMI increased by 8.0 ± 21.9 g (12.8 ± 28%, P = 0.01). The mean access blood flow did not correlate with the change in LVM in the 29 patients who underwent both echocardiograms and had flows measured at maturation and at 1 year (Figure 2). In post hoc analysis, flow at 1 month post-AV access maturation and at 1-year post-surgical creation also did not correlate with the change in LVM. None of the other subject characteristics correlated significantly with the change in LVMI (Table 2). None of the variables included in the regression analysis were predictive of the percent change in LVM although the presence of diabetes approached significance (P = 0.052). Additionally, there was no change in the left ventricle end-diastolic diameter over the 1 year of follow-up (P = 0.19) or ejection fraction (P = 0.46).

N-terminal pro-brain natriuretic peptide

Forty-two patients had two sets of BNP data. Serum NT-proBNP increased by 263.3 ± 1163 pmol/L (170 ± 465%; P = 0.02). Average access blood flow did not correlate with the percentage change in NT-proBNP (P = 0.35; Figure 3). None of the other subject characteristics significantly correlated with BNP changes (Table 2). The change in NT-proBNP did not correlate with the change in LVM (P = 0.30).

Discussion

In our 1-year prospective cohort study of 47 patients, we observed a 12.2% increase in LVM for the 38 patients with echocardiograms completed pre- and 1-year post-access creation. We also observed a 170% increase in NT-proBNP after the creation of an AVF/AVG. However, access blood flow did not correlate with increase in LVM or NT-proBNP over the 1 year of follow-up. The contribution of AV access creation to LVH has only been examined in one other prospective cohort study [16]. In that study, 12 pre-dialysis CKD patients had an AVF created and were followed up for 3 months. A significant 28-g increase in LVM was observed. Additionally, two of their patients developed an acute coronary syndrome over the study period. However, their patients had a higher baseline LVM (255 g), higher SBP and persistent extracellular fluid volume overload that may have contributed to the worsening of LVM and the clinical events observed. The contribution of access flow to the progression of LVH was not assessed directly in the study. In another prospective HD cohort study in which 298 patients underwent two echocardiograms 1 year apart, the LVMI increased by 18 g/m². However, in that study, the average haemoglobin was much lower (8.6 g/dL) and correlated with LV growth [22]. The role of the AVF in LV growth was not assessed. In a more recent study in which average blood pressure and haemoglobin values were similar to our patient population, mean LVM only increased by 1.5 g over 6 months [23]. We also observed only a small but statistically significant change in LVM over 1 year. None of the variables tested, including access flow, were associated with the percentage increase in LVM. It is unclear if just creating an AVF/AVG, independent of flow in the range examined, can have a small affect on LV remodelling. Alternatively, in patients with well-controlled blood pressure and haemoglobin, the left ventricle may be more resistant to the haemodynamic effects of an AV access. This is supported by the lack of change in the LV end-diastolic diameter and ejection fraction.

Natriuretic peptides are elevated in HD patients. BNP has been shown to positively correlate with LVMI and negatively correlate with ejection fraction [24]. Iwashima et al. studied the short-term impact of AVF creation on plasma BNP levels 10 days post-AVF creation in 16 patients with chronic kidney disease [18]. The BNP level was maximally increased (68% from baseline) at 10 days but had declined to <60% by 14 days post-access creation. In our study, the plasma level of NT-proBNP increased by 170% at 1-year post-access creation, but this change was not associated with flow through the AV access. Additionally, the change in NT-proBNP did not correlate with the change in LVM. It is unclear from our study if NT-proBNP is a marker of cardiac functional changes caused by the creation of an AVF/AVG such as LV diastolic dysfunction [18] and reduced subendocardial perfusion [25] as has been shown in other studies or is simply a marker of the loss of residual renal function over time.

There are several limitations to our study. First, a greater than anticipated number of patients did not complete the study, potentially limiting our ability to detect the importance of access flow on LV remodelling. Second, a randomized controlled trial with a CVC as the control group would have been the ideal study design but was not felt to be ethically defendable. Including a control group with a CVC access would also not have strengthened the study due to the demographic differences of the patient population that is most likely to receive a CVC, such as advanced age and existence of peripheral vascular disease [26]. Additionally, NT-proBNP levels have been shown to be higher in patients who are dialysed with a CVC [27]. Thirdly, our average access flow was approximately 1 L/min. The patient population at greatest risk for CHF may be those patients with the greater access flows as has been shown by Baille et al. [28]. In their study, 96 HD patients were questioned about symptoms compatible with cardiac failure and then had their AV access flow and cardiac output estimated with the Transonic Haemodialysis Monitor. Using a third-order polynomial regression model, they found that an access flow of >2 L/min was predictive of high-output cardiac failure. This is supported by the highest NT-proBNP values in our patients with the greatest access flows. Lastly, natriuretic peptides are affected by the type of dialysis membrane, timing of sampling (i.e. pre- versus post-HD) and residual renal function [27]. However, all of the patients in our study were dialysed with a high-flux polysulphone dialysis membrane and had the NT-proBNP measured mid-week pre-dialysis to...
minimize the impact of these variables. Loss of residual renal function was not assessed but NT-proBNP remained an important independent predictor of mortality and severe LHV in a study of chronic kidney disease and PD patients, respectively, even when the model was adjusted for residual renal function [29,30].

Conclusion

In summary, de novo congestive heart failure has a 3-year mortality of 80%. Identifying potentially modifiable risk factors for this lethal condition is, therefore, important. In a group of patients with otherwise well-controlled previously identified modifiable risk factors for congestive heart failure (SBP, DBP, anaemia and low serum albumin), we sought to determine the importance of access flow on LVM. Although there was a small increase in LVM after 1 year of follow-up post-AVF/AVG creation, the increase was not related to flow through the access. The relative increase in NT-proBNP was also not related to access flow.

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Conflict of interest statement. None declared.

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