Relationships of High Cardiac Output with Ventricular Morphology Myocardial Energetics, and Energy Costs in Patients on Hemodialysis

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Abstract

Introduction: In addition to arteriovenous fistula, patients on hemodialysis often have risks that potentially increase cardiac output (CO) such as anemia, fluid retention, and multiple vasodilator use, contributing to increased risk of high output heart failure. The aims of this study were to determine the relationships between these factors and increased CO and to evaluate the effects of the high output state on ventricular morphology, dysfunction, and myocardial energetics in patients receiving hemodialysis, using noninvasive pressure-volume loop assessment.

Methods: Cardiovascular function were assessed in hemodialysis patients with high output (EF≥50%, cardiac index [CI] >3.5L/min/m^2, n=30), those with normal output (CI ≤3.5L/min/m^2, n=205), and control subjects without ESRD (n=155).

Results: As compared to control subjects and hemodialysis patients with normal output, those with elevated output displayed decreased systemic vascular resistance (SVR) and higher ventricular contractility and heart rate. Lower hemoglobin levels were correlated with decreased SVR, greater LV contractility, and tachycardia while estimated plasma volume and inter-dialytic weight gain were associated with increased ventricular preload (end-diastolic volume), thus increasing CO. Patients with high output displayed markedly increased pressure-volume area (PVA) and PVA/stroke volume ratio, that were correlated directly with increased CO, suggesting a contribution of high output state to greater myocardial oxygen

consumption and cardiac energy costs. The use of combination vasodilator therapy (angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker and calcium channel blocker) was not associated with high output states.

Conclusion: These data provide new insights into the mechanisms underlying high output states in patients on dialysis.

Key words. cardiac output, heart failure, hemodialysis, myocardial energetics

Introduction

Heart failure (HF) is common and remains the leading cause of morbidity and mortality in patients with end stage renal disease (ESRD) on dialysis.[1] Cardiac output (CO) is usually low or normal in HF but a minority of patients have a high output state, which is termed high output HF.[2] The literature on high output HF in dialysis patients is limited to reviews and case reports mainly focusing on arteriovenous fistula (AVF).[3-5] It is well known that AVF decreases systemic vascular resistance (SVR) and simultaneously increases venous return to the heart, thus increasing CO.[6, 7] Besides AVF, hemodialysis patients often have conditions that potentially increase CO, such as fluid retention, renal anemia, and multiple vasodilator use. However, little is known how these factors contribute to high output states in this population.

A recent study has shown that arteriovenous shunt-related high output HF is associated with substantial risk of death.[2] The high output state may lead to cardiac remodeling and myocardial dysfunction that are believed to increase myocardial oxygen demands and cardiac energy costs, leading to morbidity and mortality in patients with hemodialysis. However, very little information is available regarding how elevated CO might alter ventricular structure, function, myocardial oxygen consumption, and energy costs in patients on dialysis. The pressure-volume loop assessment provides detailed information on cardiovascular function, including left ventricular (LV) contractility, arterial afterload, preload,

and myocardial energetics, and its utility in dialysis patients has been shown recently (Figure 1).[8, 9] Accordingly, the aims of the present study were (1) to elucidate relationships among fluid retention, anemia, vasodilator use, and increased CO; and (2) to determine the effects of high output states on ventricular morphology, dysfunction, and myocardial energetics in patients receiving hemodialysis.

Methods

Study population

Study participants were recruited from patients receiving hemodialysis treatment at Hidaka Hospital (Takasaki, Japan) and Gunma University Hospital (Maebashi, Japan). Some participant data from this study has been previously published,[8-10] but not as it relates to the association between CO and cardiovascular function. All subjects were hemodynamically stable and hemodialysis was performed 3 times weekly via AVFs (3-5h/day). Among 289 patients who agreed to participate in this study, we excluded patients with moderate or severe left heart valvular disease (n=14), low EF (EF<50%; n=24), severe anemia (hemoglobin<8.0 g/dl; n=1), no simultaneous blood pressure (BP) measurements (n=5), and poor echocardiographic images (n=10), remaining 235 subjects for final analyses. No participant had other alternative causes of high CO, either physiologic (pregnancy, fever, infection), congenital, or metabolic diseases. To investigate the characteristics of high output

hemodialysis patients, we categorized participants according to cardiac index (CI). Given the well-known overestimation of stroke volume (SV) by pulse Doppler echocardiography, high output state was defined by CI >3.5 L/min*m^2, and normal output was defined by CI ≤3.5 L/min*m^2, as previously reported.[2] Control subjects who not receiving hemodialysis were recruited from the echocardiographic laboratory database at the Gunma University Hospital as a comparator group (n=155). They were required to have normal EF and no left heart valvular heart disease at the echocardiographic examination (criteria above). The study protocol was approved by the institutional medical ethics committees of the two hospitals and written informed consent was obtained from all participants.

Clinical assessment

Demographic characteristics, medications, and clinical variables related to the delivery of hemodialysis were abstracted from the medical records. Blood samples were collected before starting dialysis sessions. Plasma volume was estimated by (1-hematocrit) x (a + [b x weight in kg]) where a = 1530 for men and 864 for women, and b = 41 for men and 47.9 for women, respectively.[11]

Echocardiography

Subjects were studied on their chronic medications in a hemodynamically stable state. As loading conditions can change during an inter-dialytic interval, all hemodialysis patients were studied the day before dialysis session. Echocardiographic examinations were

performed using commercially available ultrasound systems (iE33, Philips Medical System, Andover, MA; Vivid 7 dimension, GE Healthcare, Horten, Norway; or Aplio 400, TOSHIBA Medical Systems, Japan). The LV end-diastolic (EDV) and end-systolic (ESV) volumes, mass and EF were determined according to current guidelines.[12] SV was determined from the LV outflow dimension and pulse-Doppler, and was indexed to body surface area (SVI). Left atrial (LA) volume was calculated by the biapical area-length method and also indexed by body surface area. The early filling (E-wave), the peak late diastolic (A-wave) velocities and deceleration time were obtained from transmitral flow. The peak systolic (s′), early diastolic (e′) and late diastolic (a′) mitral annular velocities were recorded at the septal annulus. The ratio of early mitral diastolic inflow velocities to early diastolic mitral annular velocity (E/e′) was calculated. Systolic and diastolic BPs were measured during echocardiographic examination and end-systolic BP (0.9 × systolic BP) was calculated as previously described.[13] Arterial afterload was determined by effective arterial elastance (Ea: end-systolic BP/SV [the slope of the blue line in Figure 1]) and SVR index (SVRI: mean BP × 79.9/cardiac index). Total arterial compliance was assessed by the ratio of SV to pulse pressure. Load-independent contractility was assessed using modified single-beat method end-systolic elastance (Ees: determined from BP, SV, and pre-ejection and total systolic periods determined on LV outflow Doppler, EF, and an estimated normalized ventricular elastance at arterial end-diastole [the slope of the red line in Figure 1]), preload recruitable

stroke work (PRSW: determined from product of peak volumetric ejection rate from LV outflow Doppler and systolic BP, and EDV), and peak power index (PWRI: determined from product of peak volumetric ejection rate from LV outflow Doppler, systolic BP, and EDV).[13, 14] In the pressure-volume loop concept, stroke work is the area surrounded by the pressure-volume loop (light blue area in Figure 1), and equals to the actual external work performed by the heart. By contrast, potential energy is the area surrounded by the end-systolic pressure-volume relationship line, isovolumic relaxation phase of the pressure-volume loop, and volume axis (x-axis) (orange area in Figure 1), and it reflects energy loss that does not participate in ejection of blood into the aorta. The pressure-volume area (PVA) is the sum of the stroke work and potential energy, and has been shown to correlate linearly with myocardial oxygen consumption.[15, 16] The ratio of PVA to SV represents cardiac energy costs to produce blood flow. We estimated PVA as previously reported.[17] An experienced echocardiologist analyzed all echocardiographic measurements (MO).

Statistical analysis

All continuous variables are presented as mean ± SD unless otherwise specified. Between groups differences were compared by chi-square, ANOVA, or Kruskal-Wallis test, with Tukey's test or Steel-Dwass test for multiple comparisons. Multivariable linear regression analysis was used to adjust for baseline group differences. Two-sided $p < 0.05$ was accepted

as statistical significance. All data were analyzed using SPSS version 23.0 (SPSS Inc., Chicago, IL).

Results

Clinical Characteristics

Of hemodialysis patients, 30 patients (13%) met criteria for elevated output. Age, sex, body mass index were similar across 3 groups (Table 1). There were no significant differences in dialysis duration, the proportion of causes of ESRD, or ultrafiltration volume between hemodialysis patients with normal and elevated output. Compared with controls, patients on dialysis displayed higher prevalence of hypertension and diabetes, lower hemoglobin levels, and greater estimated plasma volume.

Relationships of Cardiac Output with Contractility, Afterload, and Preload.

Table 2 shows comparisons of cardiovascular structure and function among 3 groups. By definition, hemodialysis patients with elevated output displayed higher CI compared to those with normal output and controls. The increased CI in patients with high output was caused by both higher heart rate and SVI. As compared to hemodialysis patients with normal output and controls, those with elevated output had enhanced LV contractility (greater PRSW, PWRI, and s' velocity) and decreased systemic arterial afterload (lower SVRI and Ea and higher total arterial compliance), with more than 36% lower SVRI. Compared to

control subjects, EDV was larger in hemodialysis patients with normal output and elevated output by 8% and 14% (p=0.06), respectively, but similar between the groups. Each of these components was related to greater CO (Figure 3, total arterial compliance r=0.47, p<0.001, s' r=0.34, p<0.001, and end-diastolic volume r=0.31, p<0.001). These data suggest that the increased CO in hemodialysis patients was driven by decreased SVR, enhanced ventricular contractility, larger ventricular preload (EDV), and tachycardia. Higher mitral A-wave and a' velocity in the high output patients suggest that enhancement in atrial contraction was the main intra-cardiac mechanism which augmented LV filling and thus CO.

Contributions of Anemia and Fluid Retention to High Output States

More than 60% of patients with high output hemodialysis (n=19) had hemoglobin levels < 11.0 g/dl. Hemoglobin levels were directly correlated with SVRI (Figure 4A, r=0.38, p<0.001) and inversely correlated with heart rate (r=-0.22, p<0.0001), PWRI (-0.30, p<0.001), and thus CO (Figure 4B, r=-0.41, p<0.001). Both estimated plasma volume and inter-dialytic weight gain varied directly with EDV (Figure 4C, r=0.42 and r=0.32, both p<0.001) and CO (Figure 4D, r=0.41 and r=0.24, both p<0.001). Furthermore, SVRI and hemoglobin levels were independently associated with CO and CI (both p<0.001). These data suggest that anemia also increases CO by decreasing SVR, enhancing contractility, and/or increasing heart rate while plasma volume expansion does so by solely increasing ventricular preload.

Relationships of Cardiac Output with LV Morphology, Dysfunction, and Myocardial

Energetics

Compared with control subjects, both hemodialysis groups displayed greater LV mass index and impaired diastolic function, with higher mitral inflow E-wave, E/e' ratio, and LA volume index. The increase in CO was associated with greater LV mass index ($r=0.35$, $p<0.001$) and LA volume index ($r=0.24$, $p<0.001$). The PVA was markedly increased in hemodialysis patients with high output compared with those with normal output and control subjects, and remained significantly higher in the high output patients than those with normal output after adjusting for hemoglobin levels (both $p<0.001$). The elevation in CO was directly correlated with greater PVA (Figure 5A). Furthermore, the ratio of PVA to SV was increased in hemodialysis patients with elevated output compared with those with normal output and controls (Figure 5B), suggesting a contribution of high output state not only to greater myocardial oxygen consumption but to increased cardiac energy costs for a given SV .

Effects of Vasodilators on Cardiovascular Function

As compared with controls and hemodialysis patients with normal output, those with elevated output were more likely to be treated with angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (ACEIs/ARBs), calcium channel blockers (CCBs), and diuretics (Table 1). This indicates that vasodilator use may be associated with increased CI by reducing SVR. To explore this hypothesis, we divided hemodialysis patients into 3 groups based on vasodilator use (Supplemental table). Of hemodialysis patients, there were

107 subjects (45%) receiving combination vasodilator therapy (ACEI/ARB and CCB), and 63 (27%) those receiving either ACEI/ARB or CCB, and 65 subjects (28%) not receiving either drug. While systolic BP, pulse pressure, LV mass index, and EDV were higher in patients receiving the combination vasodilator therapy, there were no differences in arterial afterload or CI among the groups. The combination vasodilator therapy was associated with greater PVA and PVA/SV ratio, but these associations did not persist after adjusting for systolic BP, LV mass index, or systolic BP (all $p>0.7$), suggesting that arterial hypertension, LV hypertrophy, and volume expansion but not vasodilator therapy contribute to increased myocardial oxygen consumption and energy cost in dialysis patients.

Discussion

This study provides the first evaluation of relationships among fluid retention, anemia, multiple vasodilator use, and increased CO, and determines the effects of the high output state on ventricular remodeling, dysfunction, and myocardial energetics in patients receiving hemodialysis, using noninvasive pressure-volume loop assessment. As compared to hemodialysis patients with normal output, those with elevated output displayed decreased SVR, increased ventricular contractility, and tachycardia. Lower hemoglobin levels were correlated with decreased SVR, greater LV contractility, and tachycardia while fluid retention was associated with increased LV preload (EDV), contributing to increased CO. LV mass

index and diastolic function were similarly abnormal in hemodialysis patients with normal and elevated output but patients with high output displayed markedly increased PVA and PVA/SV ratio that were correlated directly with increased CO, suggesting a contribution of high output state to greater myocardial oxygen consumption and cardiac energy costs. In contrast, the combination vasodilator therapy was not associated with high output states in dialysis patients. These data provide new insights into the mechanisms underlying high output states in patients on dialysis.

Anemia and Fluid Retention – Potential Contributors to High Output States -

Arteriovenous shunt is a common cause of high output HF and shut-related high output HF is associated with substantial risk of mortality.[2] Patients on dialysis often have conditions that potentially increase CO, including the arteriovenous shunts, inter-dialytic fluid retention, renal anemia, and multiple vasodilator use. The effects of AVF on CO and cardiovascular system have been studied, but very little is known how other potential risks contribute to high output states in hemodialysis patients. In agreement with a previous invasive study examining various forms of high output HF,[2] the current data showed the increased CO in dialysis patient was related to decreased systemic arterial afterload, enhanced ventricular contractility, larger ventricular preload, and tachycardia, rather than the decreased systemic afterload alone. We further demonstrated that anemia was related to decreasing SVR, increasing heart rate, and enhancing myocardial contractility while fluid

retention correlated with increased LV preload (i.e, EDV), which contribute to high output. Anemia is common and associated with adverse cardiovascular outcomes in ESRD patients.[18] It has been reported that severe anemia (mean hemoglobin <5.0 g/dl)[19] decreases SVR by vasodilation (enhanced endothelium-derived relaxing factor and inactivation of nitric oxide) and reducing plasma viscosity, and increases heart rate to compensate oxygen delivery.[19-21] The negative relationship between hemoglobin levels and enhanced ventricular contractility may be explained by anemia-inducing catecholamine elevation.[22] Our data suggest that even mild to moderate anemia in dialysis patients (mean hemoglobin 10.6±1.0 g/dl in high output patients) relates to increases in CO.

In the current study, EDV increased directly with increases in estimated plasma volume and inter-dialytic weight gain, contributing to high output states. Volume overload is another clinical problem in dialysis patients and an important predictor of cardiovascular and all-cause deaths.[23, 24] Fluid retention in dialysis patients may be related to increased venous return due to arteriovenous shunting and accumulation of water and sodium during inter-dialytic period, where ventricular preload (i.e., EDV) is increased by nearly 50%.[8] These data reinforce the importance of appropriate management of volume status in patients on dialysis.

Effects of Increased Output on Myocardial Function

High output states in dialysis patients can lead to structural remodeling and

myocardial dysfunction.[3] However, evidence supporting this highly relies on studies comparing changes following creation of arteriovenous shunt.[6, 7] Previous studies have demonstrated that AVF creation leads to increases in LV mass, dilation of cardiac chambers (LV, RV, and LA), and worsening LV diastolic function, with increase in CO.[6, 7] In contrast, ligation of AVF was associated with LV reverse remodeling.[25, 26] In line with these results, we found direct correlation among increased CO, LV hypertrophy, and LA dilation. It is believed that the adverse remodeling and myocardial dysfunction caused by increased CO may increase myocardial oxygen demands, contributing to subsequent morbidity and mortality in patients with hemodialysis. We show for the first time that hemodialysis patients with high output had markedly increased myocardial oxygen consumption that was correlated directly with increased CO. This is consistent with prior studies.[27, 28] Buckberg et al. have reported that the formation of arteriovenous fistula in dogs increases myocardial oxygen demand and decreases oxygen supply, resulting in subendocardial ischemia.[27] In a small case series, Savage et al. have shown that myocardial oxygen consumption increases after creation of AVF while oxygen supply remains unchanged.[28] We further demonstrated that PVA/SV ratio was elevated in hemodialysis patients with elevated output. These data suggest that the high output state in dialysis patients is related not only to greater myocardial oxygen consumption but to increased cardiac energy costs to provide blood flow. Arteriovenous shunt-related high output HF is associated with substantial risk of death.[2]

Further longitudinal study is required to determine whether increased myocardial consumption and energy costs predict adverse outcomes in this population.

Clinical Implications

The current data have several important clinical implications. Vasodilators are a cornerstone in the management of hypertension and multiple vasodilators are often required to achieve optimal BP control in dialysis patients.[29] High output patients were more likely to be receiving vasodilators, forming the hypothesis that multiple vasodilator use would cause high output states in dialysis patients. However, we found that the combination vasodilator therapy (ACEI/ARB and CCB) was not associated with increased CI or excessive vasodilation.

The severity of hypertension in dialysis patients is attributed partly to volume expansion, making the management of hypertension more challenging. Despite the multiple vasodilator use, systolic BP was markedly elevated (~160 mmHg) in patients who receiving both ACEI/ARB and CCB. Because arterial afterload and contractility were similar among groups, the high systolic BP was driven by increased flow (i.e., CO) owing to fluid expansion. Our data indicate that reduction of EDV may be required to improve not only BP control but myocardial energy cost in this group of patients. It is often difficult to evaluate fluid status in patients on dialysis. The echocardiographic pressure-volume loop assessment provides information on systemic arterial afterload, ventricular preload, LV contractility, CO, and

myocardial energetics. Although the clinical benefits of treatment of hypertension in hemodialysis patients have not been established,[29] our data suggest that the noninvasive approach may be useful in the management of hypertension for patients on dialysis.

There is no proven therapy for high output HF. The treatment in dialysis patients is often challenging because it sometimes requires interventions to shunts at the expense of loss of vascular access.[30-32] We demonstrate that anemia and fluid retention in hemodialysis patients are important contributors to high output states. These data reinforce the importance of evaluation for anemia and volume status as well as AVF blood flow when high output HF is suspected.[3] Further studies are needed to determine whether therapies targeting anemia and fluid retention would improve hemodialysis patients with high output HF.

Limitations

This study has several limitations. This study was performed in two Japanese tertiary centers and as such has selection bias. Subjects were not studied invasively because of the challenges posed by the risk of invasive measurements. Therefore, we obtained pressure-volume relationship using noninvasive echocardiographic techniques. These noninvasive parameters have been well validated and have been applied to dialysis populations.[8, 9] Given the complexity of interpretation, we did not extend dose or types of vasodilators in our analyses. However, this is the first study evaluating the effect of high output on cardiovascular function in hemodialysis patients. This was cross-sectional study

and future prospective studies should be warranted to determine prognostic values of pressure-volume loop parameters in patients on dialysis

Conclusions

Decreased systemic vascular resistance, increased ventricular contractility and preload, and tachycardia contribute to high output states in patients on dialysis. Anemia increases CO by decreasing SVR, enhancing ventricular contractility, and increasing heart rate while fluid retention does so by increasing ventricular preload. The increase in CO is associated with greater myocardial oxygen consumption and cardiac energy costs. These data provide new insights into the mechanisms underlying high output states in patients on dialysis.

Disclosures:

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Figure legends

Figure 1. Pressure-volume loop relationship. Ea, effective arterial elastance; EDV, end-diastolic volume; Ees, end-systolic elastance; ESP, end-systolic pressure; ESV, end-systolic volume; and V_0, left ventricular (LV) volume at LV pressure of 0 mmHg.

Figure 2. Correlations between cardiac output (CO) and indicators of arterial afterload and LV contractility. HD, hemodialysis; PRSW, preload recruitable stroke work; PWRI, peak power index; SVRI, systemic vascular resistance index; and other abbreviations as in Figure 1.

Figure 3. (A-B) Lower hemoglobin levels were correlated with decreased SVRI and increased CO. **(C-D)** Estimated plasma volume was directly correlated with greater EDV and CO. Abbreviations as in Figures 1 and 2.

Figure 4. (A) The increase in CO was directly correlated with greater pressure-volume area (PVA). **(B)** The ratio of pressure-volume area to SV was markedly increased in hemodialysis patients with elevated output as compared to those with normal output and controls. These data suggest that high output states lead to increases in myocardial oxygen consumption and energy costs. *$p<0.05$ vs. controls and †$p<0.05$ vs. hemodialysis patients with normal output. **(C-D)** Hemodialysis patients receiving both angiotensin-converting enzyme

inhibitor/angiotensin-receptor blocker (ACEI/ARB) and calcium channel blocker (CCB) displayed greater CO and PVA as compared to those receiving either ACEI/ARB or CCB and those not receiving either. *p<0.05 vs. hemodialysis patients not receiving either ACEI/ARB or CCB and †p<0.05 vs. hemodialysis patients receiving either ACEI/ARB or CCB. Abbreviations as in Figures 2-3.