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ORIGINAL PAPER

Relationships of high cardiac output with ventricular morphology, myocardial energetics, and energy costs in hemodialysis patients with preserved ejection fraction

Tomonari Harada[1] · Masaru Obokata[1] · Koji Kurosawa[2] · Hidemi Sorimachi[1] · Kuniko Yoshida[1] · Hideki Ishida[3] · Kyoko Ito[3,4] · Tetsuya Ogawa[3,5] · Yoshitaka Ando[3] · Masahiko Kurabayashi[1] · Kazuaki Negishi[1,6,7]

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Abstract

Hemodialysis patients have conditions that increase cardiac output (CO), including arteriovenous fistula, fluid retention, vasodilator use, and anemia. We sought to determine the relationships between these factors and CO and to evaluate the effects of the high-output states on ventricular morphology, function, and myocardial energetics in hemodialysis patients, using noninvasive load-insensitive indices. Cardiovascular function was assessed in hemodialysis patients with high output [ejection fraction ≥ 50%, cardiac index (CI) > 3.5 L/min/m^2, n = 30], those with normal output (CI < 3.0 L/min/m^2, n = 161), and control subjects without hemodialysis (n = 155). As compared to control subjects and hemodialysis patients with normal CI, patients with elevated CI were anemic and displayed decreased systemic vascular resistance index (SVRI), excessive left ventricular (LV) contractility, larger LV volume, and tachycardia. Lower hemoglobin levels were correlated with decreased SVRI, excessive LV contractility, and higher heart rate, while estimated plasma volume and interdialytic weight gain were associated with larger LV volume, thus increasing CO. High output patients displayed markedly increased pressure–volume area (PVA) and PVA/stroke volume ratio, which were correlated directly with CO. The use of combination vasodilator therapy (angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker and calcium channel blocker) was not associated with high-output states. In conclusion, anemia and fluid retention are correlated with increased CO in hemodialysis patients. The high-output state is also associated with excessive myocardial work and energy cost.

Keywords Anemia · Cardiac output · Fluid retention · 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 patients on dialysis is limited to reviews and case reports mainly focusing on arteriovenous fistula (AVF) [3–5]. AVF is well known to decrease systemic vascular resistance (SVR) and simultaneously increase venous return to the heart, thus increasing CO [6, 7]. Besides AVF, hemodialysis patients often

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✉ Masaru Obokata
lady2o814@gmail.com

[1] Department of Cardiovascular Medicine, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi 371-8511, Gunma, Japan

[2] Department of Clinical Laboratory Center, Gunma University Hospital, Maebashi, Gunma, Japan

[3] Hidaka Hospital, Takasaki, Gunma, Japan

[4] Department of Nephrology, Heisei-Hidaka Clinic, Takasaki, Gunma, Japan

[5] Department of Medicine, Tokyo Women's Medical University Medical Center East, Tokyo, Japan

[6] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

[7] Nepean Clinical School, Faculty of Medicine and Health, University of Sydney, Kingswood, NSW, Australia

have conditions that potentially increase CO, including fluid retention, renal anemia, and multiple vasodilator use. However, data on how these factors contribute to high-output states in this population are limited.

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 on hemodialysis. However, limited information is available regarding how elevated CO might alter ventricular structure, function, myocardial oxygen consumption, and energy costs in patients on dialysis. Accordingly, the aims of this study were (1) to characterize cardiovascular features of high-output hemodialysis patients, (2) to elucidate relationships among fluid retention, anemia, vasodilator use, and increased CO, and (3) to determine the effects of high-output states on ventricular morphology, dysfunction, and myocardial energetics in patients receiving hemodialysis. Since ventricular loading conditions can change with increasing CO, ejection fraction (EF) may not accurately reflect systolic function. On the other hand, invasive indices of PV loops may sensitively reflect left ventricular (LV) contractility and cardiac damage than conventional EF [8]. Thus, validated noninvasive load-insensitive indices of ventricular function and performance were assessed in this study [9, 10]. We further evaluated ventricular energetics, using an echocardiography-based pressure–volume loop assessment.

Materials and methods

Study population

This was a retrospective cross-sectional study, and the study participants recruited were among patients receiving hemodialysis treatment at Hidaka Hospital (Takasaki, Japan) and Gunma University Hospital (Maebashi, Japan). Some data of the participants from this study have been previously published [9–11], but not as they relate to the association between CO and cardiovascular function. All subjects were hemodynamically stable, and hemodialysis was performed three times weekly via AVFs (3–5 h/day). Among the 288 patients who agreed to participate in this study, patients with moderate or severe left heart valvular disease (n = 14), low EF (EF < 50%; n = 24), no simultaneous blood pressure (BP) measurements (n = 5), and poor echocardiographic images (n = 10) were excluded, with 235 hemodialysis patients remaining. 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, the primary analysis was performed in patients with high-output state, which was defined by cardiac index (CI) of > 3.5 L/min/m^2 [2], compared to those with CI < 3.0 L/min/m^2 (normal CI group). Patients with intermediate CI between 3.0 and 3.5 L/min/m^2 were considered to represent an intermediate phenotype and were included in sensitivity analyses. The control subjects (n = 155) who were not receiving hemodialysis were recruited from the echocardiographic laboratory database at the Gunma University Hospital. 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 prior to the study.

Clinical assessment

Demographic characteristics, medications, and clinical variables related to the delivery of hemodialysis were collected from the medical records. Blood samples were collected prior to the start of dialysis sessions. The plasma volume was estimated using the following formula: (1-hematocrit) × (a + [b × weight in kg]), where a = 1530 for men and 864 for women and b = 41 for men and 47.9 for women, respectively [12].

Echocardiography

Subjects were investigated on their chronic medications in a hemodynamically stable state. Echocardiographic examinations were performed using commercially available ultrasound systems on the day before dialysis session. The LV end-diastolic (EDV) and end-systolic (ESV) volumes, mass, and EF were determined according to current guidelines [13]. SV was calculated using measurements of the LV outflow dimension and pulse-Doppler. LV volumes, mass, and SV were indexed to body surface area. The left atrial (LA) volume was calculated using 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 [14]. Arterial afterload was measured using effective arterial elastance [Ea: end-systolic BP/SV (the slope of the blue line in Fig. 1)] and SVR index (SVRI: mean BP × 79.9/CI). The total arterial compliance was assessed using the ratio of SV to pulse pressure. We assessed three load-insensitive measures of LV

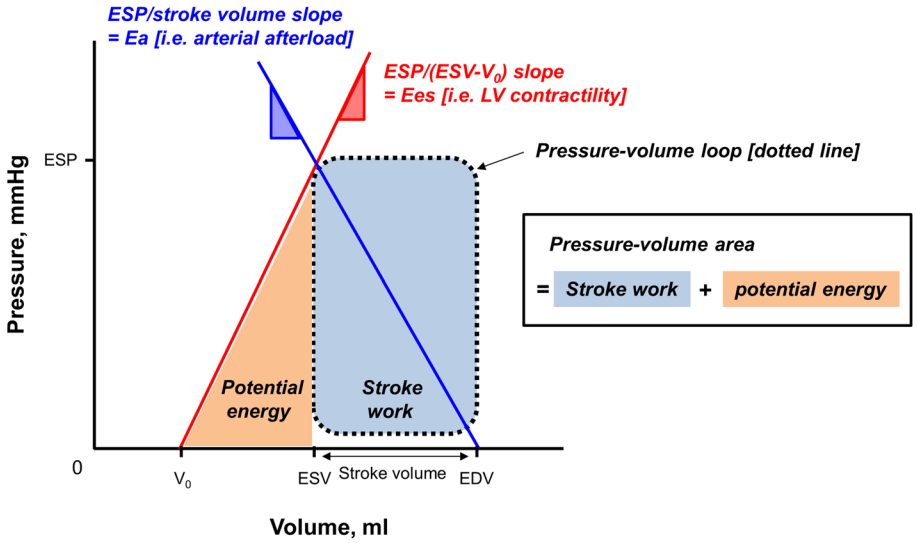

Fig. 1 Pressure–volume loop relationship. *Ea* effective arterial elastance, *EDV* end-diastolic volume, *Ees* end-systolic elastance, *ESP* end-systolic pressure, *ESV* end-systolic volume, V_0 left ventricular (LV) volume at LV pressure of 0 mmHg

systolic function. End-systolic elastance (Ees) is the positive slope (red line in Fig. 1) which reflects load-independent LV contractility and passive chamber stiffness. We estimated the Ees using the modified single-beat technique [14, 15]:

$\text{Ees} = [\text{Diastolic BP} - (E_{Nd(est)} \times \text{ESP})]/[E_{Nd(est)} \times \text{SV}]$ where $E_{Nd(est)} = 0.0275 - 0.165 \times \text{EF} + 0.3656 \times (\text{DBP}/\text{ESP}) + 0.515 \times E_{Nd(avg)}$ and $E_{Nd(avg)} = 0.35695 - 7.2266 \times (\text{PEP}/\text{SEP}) + 74.249 \times (\text{PEP}/\text{SEP})^2 - 307.39 \times (\text{PEP}/\text{SEP})^3 + 684.54 \times (\text{PEP}/\text{SEP})^4 - 856.92 \times (\text{PEP}/\text{SEP})^5 + 571.95 \times (\text{PEP}/\text{SEP})^6 - 159.1 \times (\text{PEP}/\text{SEP})^7$, and pre-ejection (PEP) and total systolic periods (SEP) were determined on LV outflow Doppler.

Preload recruitable stroke work (PRSW) was determined from stroke woke/[EDV − k × EDV + (1 − k) × LV wall volume], where stroke work (SW) = SV × mean BP, LV wall volume = LV mass/1.05, and k was assumed to be 0.7 [10]. Lastly, peak power index (PWRI) was calculated as: (peak LV outflow velocity × LV outflow area × systolic BP)/EDV [14].

In a subset of patients with DICOM-format data (n = 361, 93% of the whole population), LV deformation analyses were also performed offline with vendor-independent 2D speckle tracking software (TomTec Imaging Systems, Unterschleissheim, Germany). Global longitudinal strain (GLS) was obtained by averaging peak longitudinal strains from the four- and two-chamber views and were expressed as absolute values.

We further evaluated ventricular energetics, using an echocardiography-based pressure–volume loop assessment. In the pressure–volume loop concept, stroke work is the area surrounded by the pressure–volume loop (light blue area in Fig. 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 Fig. 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 [16, 17]. The ratio of PVA to SV represents cardiac energy costs to produce blood flow. PVA was estimated as previously reported: PVA = 0.5 × ESP × [SV + (EDV − V_0)], V_0 = ESV − ESP/Ees [18]. This echocardiographic pressure–volume loop assessment has been shown to have good reproducibility in our laboratory [10]. All echocardiographic measurements were analyzed by an experienced investigator (MO).

Statistical analysis

All continuous variables are presented as mean ± SD unless otherwise specified. Between-group differences were analyzed using Chi square, ANOVA, or Kruskal–Wallis test, and Tukey's test or Steel–Dwass test was used for multiple comparisons. Pearson's or Spearman's analyses were used to assess correlations, as appropriate. The multivariable linear regression analysis was used to adjust for baseline group differences. Two-sided $p < 0.05$ was considered as statistical significant. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY).

Results

Clinical characteristics

Among the hemodialysis patients, 30 patients (13%) met criteria for elevated output. Data on age, sex, and

body mass index were similar across the three groups (Table 1). Mean estimated glomerular filtration rate was 74 ± 22 mL/min/1.73 m^2 in control subjects. No significant differences were observed in dialysis duration, the proportion of ESRD causes, or ultrafiltration volume between hemodialysis patients with normal and elevated output. Compared with controls, patients on dialysis displayed higher prevalence of hypertension, lower hemoglobin levels, and greater estimated plasma volume. Hemoglobin levels were much lower in patients with high-output than those with normal output, and more than 60% of patients with high-output hemodialysis (n = 19) had hemoglobin levels of < 11.0 g/dl.

Relationships of cardiac output with contractility, afterload, and preload

Table 2 shows comparisons of cardiovascular structure and function among the three 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 index was larger in hemodialysis patients with

Table 1 Clinical characteristics

Characteristics	Controls (n = 155)	HD with normal CI (n = 161)	HD with elevated CI (n = 30)	p Value[#]
Age, years	67 ± 10	65 ± 11	65 ± 12	0.51
Male gender	116 (75%)	119 (74%)	22 (73%)	0.97
Body weight, kg	60 ± 11	60 ± 13	61 ± 12	0.97
Dry weight, kg	–	59 ± 12	57 ± 12	0.61
Body mass index, kg/m^2	22.9 ± 3.0	22.5 ± 3.6	23.6 ± 3.4	0.21
Dialysis duration, years	–	5.8 (1.9–11.9)	5.6(3.4–9.7)	0.61
Cause of ESRD				
Diabetes	–	71 (44%)	13 (43%)	0.30
Glomerulonephritis	–	50 (31%)	14 (47%)	
Cystic kidney disease	–	11 (7%)	1 (3%)	
Hypertension	–	11 (7%)	0 (0%)	
Other	–	18 (11%)	2 (7%)	
Blood flow rate, mL/min	–	196 ± 27	202 ± 30	0.34
Ultrafiltration volume, mL	–	2664 ± 1204	2890 ± 1081	0.35
Comorbidities				
Hypertension	87 (56%)	134 (83%)*	27 (90%)*	< 0.001
Diabetes	45 (29%)	77 (48%)*	15 (50%)	0.001
Dyslipidemia	65 (42%)	50 (31%)	10 (33%)	0.12
Current smoker	24 (16%)	28 (17%)	5 (17%)	0.93
Coronary artery disease	44 (29%)	38 (24%)	3 (10%)	0.09
Medications				
ACEIs/ARBs	50 (32%)	90 (56%)*	24 (80%)*,†	< 0.001
Beta blockers	28 (18%)	50 (31%)*	4 (13%)	0.01
Calcium channel blockers	52 (34%)	83 (52%)*	25 (83%)*,†	< 0.001
Diuretics	12 (8%)	36 (22%)*	8 (27%)*	< 0.001
Hemoglobin, g/dl	13.2 ± 1.7	11.2 ± 1.2*	10.6 ± 1.0*,†	< 0.001
Estimated plasma volume, mL	2362 ± 311	2586 ± 425*	2683 ± 435*	< 0.001

Values are mean ± SD. Median (interquartile range), or n (%)

ACEIs/ARBs angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, *BP* blood pressure, *CI* cardiac index, *ESRD* end-stage renal disease, *HD* hemodialysis

[#]The p values reflect overall group analysis using Chi square, ANOVA, or Kruskal–Wallis test

*p < 0.05 versus controls

[†]p < 0.05 versus hemodialysis patients with normal cardiac index

Table 2 Cardiovascular structure and function

Characteristics	Controls (n = 155)	HD with normal CI (n = 161)	HD with elevated CI (n = 30)	p Value[#]
Hemodynamics				
Systolic BP, mmHg	139 ± 21	159 ± 30*	176 ± 27*,†	< 0.001
Diastolic BP, mmHg	76 ± 12	76 ± 16	78 ± 19	0.75
Mean BP, mmHg	97 ± 14	104 ± 19*	110 ± 19*	< 0.001
Pulse pressure, mmHg	63 ± 18	82 ± 22*	98 ± 23*,†	< 0.001
Heart rate, beats/min	65 ± 13	70 ± 10*	77 ± 10*,†	< 0.001
LV structures and volumes				
LV mass index, g/m^2	91 ± 23	116 ± 30*	127 ± 25*	< 0.001
End-diastolic volume index, mL/m^2	49 ± 11	51 ± 14	56 ± 10*	0.007
End-systolic volume index, mL/m^2	18 ± 6	18 ± 7	19 ± 7	0.65
Contractility				
Ees, mmHg/mL	4.7 ± 1.7	4.7 ± 1.7	3.4 ± 1.0*,†	< 0.001
PRSW, g/cm^2	72 ± 26	73 ± 20	110 ± 23*,†	< 0.001
Peak power index, g/s	436 ± 175	516 ± 169*	773 ± 189*,†	< 0.001
s′ velocity, m/s	7.2 ± 1.5	7.3 ± 1.7	8.6 ± 1.5*,†	< 0.001
GLS, % (n = 150/147/26)	20.3 ± 3.8	17.0 ± 4.1*	18.5 ± 3.2	< 0.0001
Arterial afterload				
Ea, mmHg/mL	2.9 ± 0.9	2.8 ± 0.8	2.0 ± 0.5*,†	< 0.001
SVRI, dyne s^{-1} m^2 cm^{-5}	4,511 ± 1,609	3,790 ± 1,099*	2,263 ± 463*,†	< 0.001
Total arterial compliance, mL/mmHg	0.8 ± 0.3	0.7 ± 0.3*	0.9 ± 0.5†	< 0.001
Diastolic function				
Mitral inflow E-wave, m/s	66 ± 16	76 ± 23*	85 ± 21*,†	< 0.001
Mitral inflow A-wave, m/s	78 ± 19	97 ± 23*	115 ± 17*,†	< 0.001
Deceleration time, ms	219 ± 62	245 ± 76*	238 ± 63	0.003
e′ velocity, m/s	6.1 ± 1.8	5.4 ± 1.5*	6.0 ± 1.2	0.001
a′ velocity, m/s	9.6 ± 1.9	9.3 ± 1.8	11.0 ± 1.9*,†	< 0.001
E/e′ ratio	11.4 ± 3.5	14.7 ± 5.4*	14.3 ± 3.0*	< 0.001
LA volume index, mL/m^2	28 ± 10	38 ± 13*	39 ± 11*	< 0.001
Integrated parameters				
Ejection fraction, %	64 ± 7	66 ± 7*	67 ± 8	0.02
Stroke volume index, mL/m^2	29 ± 8	34 ± 8*	52 ± 10*,†	< 0.001
Cardiac index, L/min/m^2	1.9 ± 0.6	2.3 ± 0.5*	3.9 ± 0.5*,†	< 0.001

Values are mean ± SD. Final column reflects overall analysis

a′ late diastolic mitral annular velocity, *e′* early diastolic mitral annular velocity, *Ea* arterial elastance, *Ees* end-systolic elastance, *GLS* left ventricular global longitudinal strain, *LA* left atrial, *LV* left ventricular, *PRSW* preload recruitable stroke work, *s′* systolic mitral annular velocity, *SVRI* systemic vascular resistance index

[#]The p values reflect overall group analysis using ANOVA, or Kruskal–Wallis test

*p < 0.05 versus controls

†p < 0.05 versus hemodialysis patients with normal cardiac index

elevated output. Each of these components was related to greater CO (Fig. 2, SVRI $r^2 = 0.65$ by definition, total arterial compliance r = 0.46, p < 0.001, s′ r = 0.33, p < 0.001, and end-diastolic volume r = 0.30, p < 0.001). These data suggest that the increased CO in hemodialysis patients was driven by decreased arterial afterload, enhanced ventricular contractility, larger ventricular preload (EDV index), and tachycardia. In contrast, GLS was significantly lower in patients on dialysis than control subjects (17.2 ± 4.1% vs. 20.3 ± 3.8%, p < 0.0001). Higher mitral A-wave and a′ velocity in the high-output patients suggest that enhancement in atrial contraction augments LV filling and thus CO.

Contributions of anemia and fluid retention to high-output states

Hemoglobin levels were directly correlated with SVRI (Fig. 3a, r = 0.37, p < 0.001) and inversely correlated

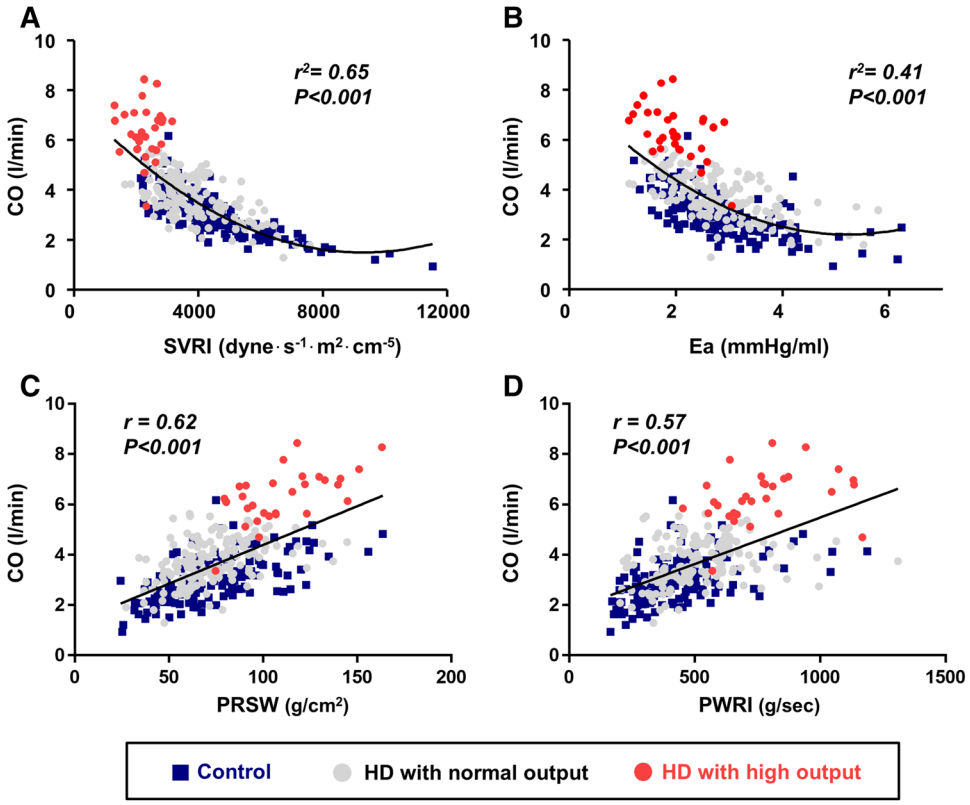

Fig. 2 Correlations between cardiac output (CO) and indicators of arterial afterload and LV contractility. *HD* hemodialysis, *PRSW* preload recruitable stroke work, *PWRI* peak power index, *SVRI* systemic vascular resistance index; and other abbreviations as in Fig. 1

with heart rate ($r=-0.22$, $p<0.0001$), PWRI ($r=-0.29$, $p<0.001$), and thus CO (Fig. 3b, $r=-0.38$, $p<0.001$). Both estimated plasma volume and interdialytic weight gain varied directly with EDV (Fig. 3c, $r=0.46$ and $r=0.33$, both $p<0.001$) and CO (Fig. 3d, $r=0.41$ and $r=0.26$, 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 might relate to higher CO by decreasing SVR, enhancing contractility, and/or increasing heart rate while plasma volume expansion does so by solely increasing ventricular preload.

Vasodilators and cardiac output

As compared with the 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) and calcium channel blockers (CCBs) (Table 1). This indicates that vasodilator use may be associated with increased CI by reducing SVR. To explore this hypothesis, hemodialysis patients were divided into three groups based on vasodilator use (Table 3). Of the hemodialysis patients, a total of 85 subjects (45%) received combination vasodilator therapy (ACEI/ARB and CCB), and 52 subjects (27%) received either ACEI/ARB or CCB, and 54 subjects (28%) did not receive either drug. While systolic BP, mean BP, pulse pressure, and LV mass index were higher in patients treated with the combination vasodilator therapy than those with no vasodilator, there were no differences in arterial afterload or CI among the groups.

Relationships of cardiac output with LV morphology, dysfunction, and myocardial energetics

As shown in Table 2, both hemodialysis groups displayed greater LV mass index and impaired diastolic function compared with the control subjects, evidenced by higher mitral inflow E-wave, E/e′ ratio, and LA volume index. The increase in CO was associated with greater LV mass index ($r=0.32$, $p<0.001$) and LA volume index ($r=0.20$, $p<0.001$). The PVA was markedly increased in hemodialysis patients with high output compared with those with normal output and control subjects ($17{,}364\pm4666$ mmHg mL*,† vs. $10{,}263\pm3537$ mmHg mL*, and $7{,}739\pm2603$ mmHg mL; overall $p<0.001$, $^{*}p<0.05$ versus controls, and $^{\dagger}p<0.05$ versus hemodialysis patients with normal CI). The PVA 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 (Fig. 4a). Furthermore, the ratio of PVA to SV was increased in hemodialysis patients with elevated output than in those with normal output and controls (Fig. 4b), suggesting a contribution of high-output state

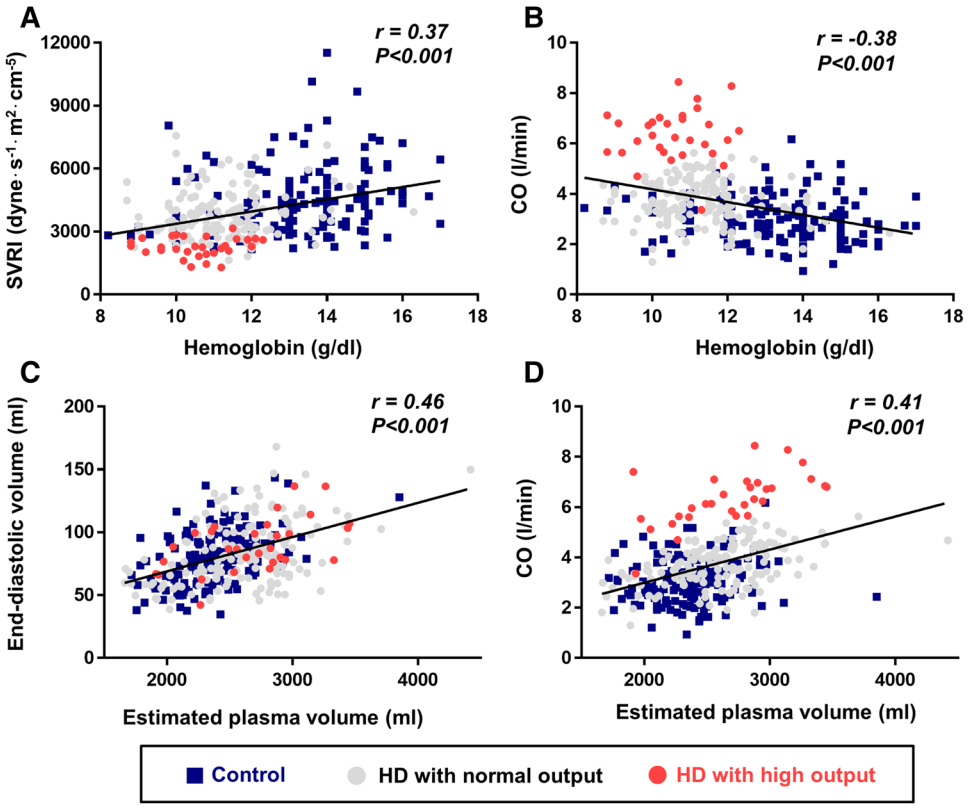

Fig. 3 **a, b** Lower hemoglobin levels were correlated with decreased SVRI and increased CO. **c, d** Estimated plasma volume was directly correlated with greater EDV and CO. Abbreviations as in Fig. 2

not only to greater myocardial oxygen consumption but also to increased cardiac energy costs for a given SV.

Sensitivity analysis

Patients with a CI between 3.0 and 3.5 L/min/m^2 had intermediate cardiovascular features between those with CI < 3.0 L/min/m^2 and those with high-output (Supplemental Table 1). Importantly, the observed correlations between CO, arterial afterload, LV contractility, hemoglobin levels, and plasma volume remained significant after including the patients with intermediate CI (Supplemental Figs. 1, 2).

Discussion

This study characterized the clinical and cardiovascular features of hemodialysis patients with elevated CO, using noninvasive load-insensitive indices. As compared to controls and patients with normal output, those with elevated output were anemic and displayed decreased arterial resistance, larger LV volume, excessive contractility, and tachycardia. Lower hemoglobin levels were correlated with the decreased SVRI, excessive contractility, and tachycardia, while fluid retention was associated with the larger LV volume (preload), contributing to the increased CO. In contrast, the combination vasodilator therapy was not associated with high-output states in patients on dialysis. While LV mass index and diastolic function were similarly abnormal in hemodialysis patients with normal and elevated output, those 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. Although causality cannot be assessed from this cross-sectional study, these data provide new insights into the mechanisms underlying high-output states in patients on dialysis and a number of clinical implications.

Anemia and fluid retention: potential contributors to high-output states

Arteriovenous shunt is a common cause of high-output HF, and shunt-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, interdialytic fluid retention, renal anemia, and the use of multiple vasodilators. The effects of AVF on CO and cardiovascular system have been studied, but data on how other potential risks contribute to high-output states in hemodialysis patients are limited. In agreement with a previous invasive study examining various forms of high-output HF [2], the current data showed that the increased CO in patients on dialysis was related to decreased

Table 3 Cardiovascular structure and function in hemodialysis patients according to vasodilator therapy

Characteristics	No vasodilator (n = 54)	ACEI/ARB or CCB (n = 52)	ACEI/ARB and CCB (n = 85)	p Value[#]
Clinical characteristics				
Age, years	66 ± 11	64 ± 11	66 ± 11	0.66
Male gender	44 (82%)	30 (58%)*	67 (79%)[†]	0.008
Body mass index, kg/m^2	22.7 ± 3.4	22.3 ± 3.9	22.9 ± 3.5	0.69
Hemodynamics				
Systolic BP, mmHg	154 ± 27	157 ± 31	168 ± 29*	0.011
Diastolic BP, mmHg	74 ± 15	76 ± 18	78 ± 16	0.27
Mean BP, mmHg	101 ± 18	103 ± 20	108 ± 18*	0.04
Pulse pressure, mmHg	80 ± 19	82 ± 24	90 ± 24*	0.02
Heart rate, beats/min	71 ± 8	71 ± 12	71 ± 11	0.98
LV structures and volumes				
LV mass index, g/m^2	112 ± 28	112 ± 28	125 ± 29*,[†]	0.008
End-diastolic volume index, mL/m^2	49 ± 14	52 ± 14	54 ± 13	0.07
End-systolic volume index, mL/m^2	17 ± 7	18 ± 8	19 ± 7	0.13
Contractility				
Ees, mmHg/mL	4.3 ± 1.4	5.0 ± 1.9	4.3 ± 1.7[†]	0.04
PRSW, g/cm^2	80 ± 24	76 ± 24	80 ± 25	0.58
Peak power index, g/s	570 ± 182	506 ± 178	583 ± 208	0.08
s′ velocity, m/s	7.5 ± 1.8	7.4 ± 1.6	7.6 ± 1.7	0.75
GLS, % (n = 49/49/75)	17.4 ± 4.5	16.5 ± 4.2	17.6 ± 3.7	0.29
Arterial afterload				
Ea, mmHg/mL	2.6 ± 0.7	2.8 ± 1.0	2.6 ± 0.8	0.30
SVRI, dyne s^{-1} m^2 cm^{-5}	3391 ± 859	3713 ± 1302	3563 ± 1241	0.54
Total arterial compliance, mL/mmHg	0.7 ± 0.2	0.7 ± 0.3	0.7 ± 0.4	0.48
Diastolic function				
Mitral inflow E-wave, m/s	73 ± 21	80 ± 26	76 ± 21	0.32
Mitral inflow A-wave, m/s	96 ± 23	96 ± 24	104 ± 22	0.07
Deceleration time, ms	252 ± 76	235 ± 62	249 ± 78	0.72
e′ velocity, m/s	5.5 ± 1.5	5.7 ± 1.4	5.3 ± 1.3	0.11
a′ velocity, m/s	9.3 ± 1.7	9.4 ± 2.0	9.9 ± 1.9	0.07
E/e′ ratio	13.8 ± 4.9	14.7 ± 6.3	15.2 ± 4.6	0.08
LA volume index, mL/m^2	35 ± 12	38 ± 13	39 ± 13	0.28
Integrated parameters				
Ejection fraction, %	67 ± 7	67 ± 8	65 ± 7	0.59
Stroke volume index, mL/m^2	36 ± 8	35 ± 12	38 ± 11	0.18
Cardiac index, L/min/m^2	2.5 ± 0.5	2.5 ± 0.8	2.7 ± 0.9	0.12

Values are mean ± SD or n (%). Abbreviations as in Tables 1 and 2

[#]The p values reflect overall group analysis using Chi square, ANOVA, or Kruskal–Wallis test

*$p < 0.05$ versus hemodialysis patients not receiving any vasodilator

[†]$p < 0.05$ versus hemodialysis patients receiving either ACEI/ARB or CCB

systemic arterial afterload, excessive LV contractility, larger LV preload, and tachycardia rather than the decreased systemic afterload alone. We further demonstrated that anemia was related to decreasing SVRI, increasing heart rate, and enhancing myocardial contractility, while fluid retention correlated with increased LV preload (i.e., EDV), which contributes to high output.

Anemia is common and associated with adverse cardiovascular outcomes in patients with ESRD [19]. In the current study, hemoglobin levels were the lowest in hemodialysis patients with high-output, and lower hemoglobin levels were correlated with higher CO. Our data suggest that even mild to moderate anemia in patients on dialysis (mean hemoglobin of 10.6 ± 1.0 g/dl in high-output patients) can

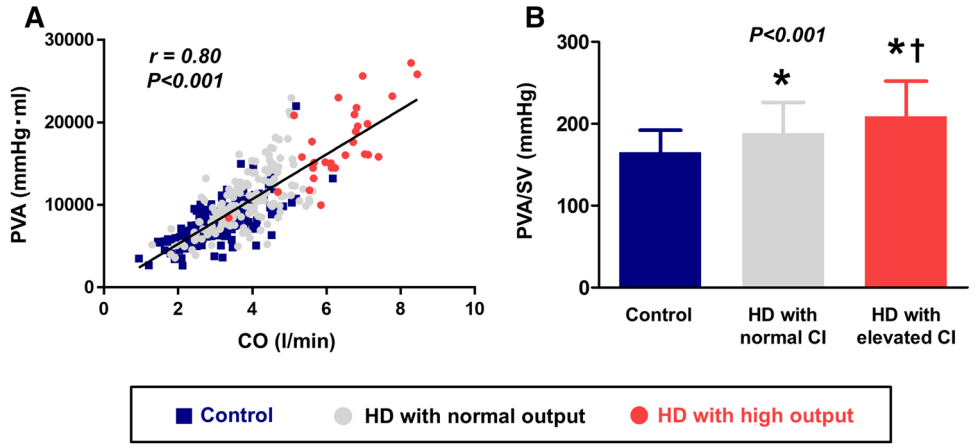

Fig. 4 **a** The increase in CO was directly correlated with greater pressure–volume area (PVA). **b** The ratio of pressure–volume area to stroke volume (SV) was markedly increased in hemodialysis patients with elevated output as compared to those with normal output and controls. These data suggest that high-output states lead to increases in myocardial oxygen consumption and energy costs. *$p < 0.05$ versus controls and $^{\dagger}p < 0.05$ versus hemodialysis patients with normal output. *CI* cardiac index; and other abbreviations as in Fig. 2

lead to high-output states. Severe anemia has been reported (mean hemoglobin of < 5.0 g/dl) [20] to decrease SVR via vasodilation (enhanced endothelium-derived relaxing factor and inactivation of nitric oxide) and reduction of plasma viscosity and increase heart rate to compensate oxygen delivery [20–22]. The negative relationship between hemoglobin levels and excessive ventricular contractility may be explained by anemia-inducing catecholamine elevation [23]. It is worth pointing out that the excessive contractility was accompanied by increased LV myocardial oxygen consumption and cardiac energy costs.

Unlike the other contractile parameters, Ees was lower in patients with high output than those with normal output and controls. Ees is not a pure measure of contractility and it is influenced by chamber geometry and passive stiffness [24]. In hypertensive heart diseases, patients with HFpEF, and dialysis patients, Ees increases with increasing vascular afterload (i.e., Ea) in order to maintain ventricular-arterial coupling. This increased Ees however goes together with impaired contractile performance. Therefore, there is a well-known dissociation between contractility and systolic LV elastance (i.e., high Ees but low contractility). Conversely, in patients with high-output states, decreased Ees could be an adequate response to decreased Ea. We also found that GLS was lower in hemodialysis patients than control subjects. This suggests subtle impairments in LV shortening despite having enhanced ventricular contraction. Further study is needed to understand the pathophysiological meaning of each echocardiographic parameter reflecting LV systolic function.

In the current study, EDV increased directly with increases in estimated plasma volume and interdialytic weight gain, contributing to high-output states. Volume overload is another clinical problem in patients on dialysis and an important predictor of cardiovascular and all-cause deaths [25, 26]. Fluid retention in patients on dialysis may be related to increased venous return due to arteriovenous shunting and accumulation of water and sodium during interdialytic period, where ventricular preload (i.e., EDV) is increased by nearly 50% [9]. We observed the correlation between interdialytic weight gain and CO. This suggests that interdialytic weight gain may be a therapeutic target for not only volume status but also high-output states in patients on dialysis.

Effects of increased output on myocardial function

High-output states in patients on dialysis 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 [27, 28]. In line with these results, a direct correlation was found among increased CO, LV hypertrophy, and LA dilation in this study. The adverse remodeling and myocardial dysfunction caused by increased CO are believed to increase myocardial oxygen demands, contributing to subsequent morbidity and mortality in patients with hemodialysis. Consistent with prior studies [29, 30], we found that hemodialysis patients with high output had markedly increased myocardial oxygen consumption that was correlated directly with increased CO. We further demonstrated that PVA/SV ratio, a marker

of myocardial energy cost, was elevated in hemodialysis patients with elevated output. While causality cannot be assessed from this cross sectional study, these data suggest that the high-output state in patients on dialysis is related not only to greater myocardial oxygen consumption but to increased cardiac energy costs to provide blood flow. Further study is needed 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 patients on dialysis [31]. High-output patients were more likely to be receiving vasodilators, forming the hypothesis that multiple vasodilator use would cause high-output states in patients on dialysis. However, the combination vasodilator therapy (ACEI/ARB and CCB) was not associated with increased CI or excessive vasodilation.

No proven therapy is currently available for high-output HF. The treatment in patients on dialysis is often challenging because it sometimes requires interventions to shunts at the expense of loss of vascular access [32–34]. In the current study, anemia and fluid retention in hemodialysis patients were 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 necessary 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, pressure–volume relationship using noninvasive echocardiographic techniques was obtained. These noninvasive parameters have been well validated and have been applied to dialysis populations [9, 10]. Given the complexity of interpretation, dose or types of vasodilators in our analyses were not extended. The number of hemodialysis patients with high output was relatively small (n = 30). We did not have data on residual renal function and could not assess its effect on interdialytic weight gain and CO. While AVF might affect CO in dialysis patients, data on AVF flow were not available. Thus we cannot determine how AVF flow rates influenced the results observed. However, this is the first study evaluating the effect of high output on cardiovascular function in hemodialysis patients. This was a cross-sectional study, and future prospective studies should be warranted to determine prognostic values of pressure–volume loop parameters in patients on dialysis.

Conclusions

Anemia and fluid retention but multiple vasodilator use are associated with high output. 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.

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Compliance with ethical standards

Conflict of interest Dr. Obokata received research funding from Kureha Corporation, Tokyo, Japan. The sponsors were not involved in the study design, data collection, analysis and interpretation, and preparation of the manuscript.

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