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ORIGINAL INVESTIGATION

Echocardiography Detects Elevated Left Ventricular Filling Pressures in Heart Transplant Recipients

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Diastolic dysfunction is a recognized complication in heart transplant (HTx) recipients that limits exercise capacity and is a risk factor for mortality. We investigated the ability of echocardiography to detect elevated pulmonary capillary wedge pressure (mean PCWP>15 mmHg) in HTx recipients. This retrospective study comprised HTx recipients with echocardiography and right heart catheterization within 24 hours (n = 100, 113 investigations). Echocardiographic assessment was performed using mitral inflow (E/A ratio, deceleration time [DT], isovolumic relaxation time [IVRT]), tissue Doppler (E/E′ lateral) parameters, and the Doppler-estimated pulmonary artery systolic pressure (Doppler PASP). The right atrial pressure (RAP) was estimated based on size and the effect of respiration or sniffing on the inferior vena cava diameter. Cutoff values were determined from a derivation group (n = 57, receiver operator characteristic curve analysis) and evaluated in a test group (n = 56). Elevated PCWP were found in 38%. The RAP and PCWP were both normal in 58 investigations and elevated in 39 investigations (concordance rate of 86.6%). The presence of signs of increased RAP by echocardiography or with three of five parameters (E/A, DT, IVRT, E/E′ lateral, and Doppler PASP) reaching the cutoff values ruled in elevated PCWP with positive likelihood ratios ranging from 15.3 to 9. With normal RAP by echocardiography or none of the other parameters reaching cutoff values elevated PCWP can be ruled out with negative likelihood ratios ranging from 0.07 to 0.19. In conclusion, elevated PCWP in HTx recipients can be assessed using echocardiography. (Echocardiography 2014;00:1–9)

Key words: heart transplant recipient, echocardiography, diastolic dysfunction

Heart transplant (HTx) recipients have reduced functional capacity following otherwise successful operations.[1,2] The reason for this is multifactorial and possible explanations include disturbed regulation of peripheral blood flow, skeletal muscle dysfunction, sympathetic denervation leading to chronotropic incompetence, and left ventricular diastolic dysfunction.[2] The diastolic dysfunction itself results from the combination of several factors, and is a common finding early after transplantation[3] due to hypervolemia, mismatch between the donor's heart size and recipient's body size, effect of organ ischemia, and early rejection.[4] After the first postoperative weeks, the incidence of diastolic dysfunction and elevated filling pressures decrease, and the diastolic dysfunction observed later is likely due to the number of rejection episodes, hypertension, and myocardial ischemia from cardiac allograft vasculopathy. Diastolic dysfunction, especially with right ventricular (RV) involvement occurring in the first year following transplantation[5] and in patients with acute rejection[6] is a known risk factor for increased mortality. Assessment of left ventricular filling pressure by echocardiography in HTx recipients is challenging and the results from studies are conflicting. Mitral inflow and pulmonary venous Doppler measurements have not been shown to predict pulmonary capillary wedge pressure (PCWP) in transplant recipients[7] and tissue Doppler measurements are considered useful by some investigators[8] but not by others.[9] The current recommendations for assessment of diastolic dysfunction do not discuss HTx recipients.[10]

In this study, we investigate the ability of echocardiography to identify HTx recipients with elevated filling pressure in the left ventricle.

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Methods:

Study Population:

This retrospective study comprised 100 HTx recipients investigated with Doppler echocardi-

ography and right heart catheterization (RHC) on 113 occasions at the King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom of Saudi Arabia. The investigations were performed from 2006 to 2013 with 40 patients investigated from 2006 to 2009. The inclusion criteria were (1) regular cardiac rhythm and (2) RHC within 24 hours of Doppler echocardiography. The total number of HTx recipients screened was 133. The reason for exclusion (n = 33) was to long time period between RHC and echocardiography. No patient was excluded due to missing data. All the patients were operated with the bicaval method.

The Ethics Committee at the King Faisal Specialist Hospital & Research Center approved the study.

Doppler Echocardiography:
The left ventricular diastolic volume and ejection fraction were measured using the Simpson's method. The thickness of the interventricular septum and posterior wall were measured using M-mode from the parasternal view, or if not possible, by two-dimensional echocardiography. The RV area was traced in diastole and systole. The fractional area change (FAC) was calculated [$FAC = (RV_{diastole} - RV_{systole})/RV_{diastole} \times 100$].
Mitral and pulmonary vein flow were recorded with pulsed Doppler placed between the tips of the valves and the right upper pulmonary vein, respectively. The ratio between early (E) and late (A) mitral inflow was calculated (E/A) and the E-wave deceleration time (DT) was measured. In order to measure the isovolumic relaxation time (IVRT), the pulsed Doppler sample volume was positioned in the left ventricular outflow tract aiming at recording the aortic valve closure and the mitral inflow simultaneously. The IVRT was measured from the leading edge of the click due to aortic valve closure and the leading edge of the onset of mitral velocity recording. The ratio between pulmonary vein peak systolic (S) and diastolic (D) velocities was calculated (S/D). Tissue spectral Doppler recordings were performed in the septal and lateral annular plane. The tissue velocity in early (E′) diastole was measured and the E/E′ ratio was calculated for the septal and lateral wall. The end systolic volume of the left atrium was calculated using the area-length method. All Doppler measurements were performed off line with a sweep speed of 75–200 mm/sec. The measurements were performed on three consecutive RR intervals.

Echocardiographic estimation of the right atrial pressure (RAP) was performed by inspection of the inferior vena cava (IVC) with the patient in recumbent position. The RAP was divided into categories based on the size and collapsibility of the IVC during quiet breathing and sniffing. The RAP was considered 0 mmHg if the cava inferior was totally collapsed, being 5 mmHg if the diameter was <20 mm and decreased by >50% during quiet breathing or sniffing (=collapsible), being 10 mmHg if the diameter was <20 mm but the reduction in diameter was <50% by breathing or sniffing (=noncollapsible), being 15 mmHg if the diameter was >20 mm and it was noncollapsible and being 20 mmHg if the diameter was >25 mm without any diameter change during breathing or sniffing.[11,12] All measurements and the assessment of RAP were performed by one investigator (OB-H) with more than 20 years experience in echocardiography that was blinded to the findings on RHC.

RHC and Coronary Angiography:
The RHC was performed with the patient fasting using only local anesthesia at the site of needle puncture and without intravenous fluid during or following the procedure. A balloon wedge pressure catheter was introduced via the femoral vein using the Seldinger technique. The following variables were recorded or derived: mean RAP, pulmonary artery systolic pressure (PASP), pulmonary artery mean pressure (PAMP), mean PCWP, cardiac output, and pulmonary vascular resistance. Cardiac output was determined by the indirect Fick method. To ensure quality, the same investigator reviewed all pressure waveforms obtained. The PCWP and RAP values used were those obtained by the hemodynamic system (Siemens AXIOM Sensis, Siemens Medical Solutions, Munich, Germany) typically by averaging 5–8 heart cycles.

The first coronary angiogram was performed according to protocol approximately 1 year following transplantation. Coronary angiography was done at the same time as RHC in 11 patients and a small volume of contrast was then given after the pressure measurements.

Statistical Analysis:
Continuous variables with normal distribution are expressed as the mean ± SD and median (25 and 75 percentile) when the distribution was not normal. The degree of linear relationship between catheter measurements and echocardiography was assessed by the Pearsons correlation coefficient (R) if the data were continuous. Correlation between estimation of RAP by echocardiography in categories and results from RHC were determined using Spearman's rho. When comparing groups, the independent samples *t*-test (2-tailed) was used to compare continuous data or Mann-Whitney test when appropriate and the Fisher's exact test to compare proportions. A $P < 0.05$ was considered statistically significant. The strength of agreement between

catheter RAP and catheter PCWP was assessed by kappa. The study population was divided into a derivation group that comprised the first 57 investigations performed and a test group that comprised the following 56 investigations. Receiver operator characteristic curve analysis was performed in the derivation group to establish cutoff values for elevated PCWP (>15 mmHg). These cutoff values were used in the test group. Diagnostic utility was described using sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and odds ratio. Positive likelihood ratio is defined as the ratio between the probability of a positive test in those with disease and the probability of a positive test in those without disease [sensitivity/(1-specificity)]. Negative likelihood ratio is defined as the ratio between the probability of a negative test in a patient with disease and the probability of a negative test in a patient without disease [(1-sensitivity)/specificity]. The odds ratio is positive likelihood ratio/ negative likelihood ratio.

Results:

The mean ± SD (range) age was 36 ± 13 (range 13–60) years and 78% were male. The donor age was 35 ± 9 years (range 16–56 years). Thirty-five percent (40/113) of the echocardiography investigations were performed the same day as RHC, in 56% (63/113) echocardiography was performed the day before and in 9% (10/113) the day following RHC. When echocardiography was done the same day as RHC it was done with both investigations in the morning or afternoon in 57% and with RHC in the morning and echocardiography in the afternoon in 43%. The heart rate was significantly higher during RHC compared with echocardiography (91 ± 13 vs. 89 ± 13 bpm, P = 0.001) while the systolic (121 ± 22 vs. 122 ± 17 mmHg, P = 0.90) and diastolic (75 ± 16 vs. 74 ± 14 mmHg, P = 0.48) blood pressure was at the same level. Sixty-five percent (65/100) of the transplanted patients had dilated cardiomyopathy, 18% (18/100) had ischemic heart disease, 7% (7/100) valvular heart disease, 5% (5/100) were miscellaneous, and in 5% (5/100) the diagnosis was not established. The time interval (median, 25 and 75 percentile) between transplantation and the RHC was 239 days (96 to 355). The RHC was performed within the first month following transplantation in 13.3% (15/113) of the investigations and more than 1 year following transplantation in 20.3% (23/113). The RHC with endomyocardial biopsies were performed as a part of the routine follow-up in 96% (108/113) and due to symptoms and suspicion of rejection in 4% (5/113) of the investigations. There were no signs of rejection in 55.8% (63/113), mild cellular rejection (Grade 1R)[13] in 34.5% (39/113), moderate or severe rejection (Grade 2R/3R) in 3.5% (4/113), and humoral rejection in 2.7% (3/113). The biopsy was nondiagnostic in 3.5% (4/113). The left ventricular ejection fraction was 57 ± 11% and ≥50% in 79% of the investigations. Forty percent (40/100) of the patients had coronary angiography performed in which 25% showed evidence of coronary artery disease.

Rejection (2R/3R) was only found in patients with elevated PCWP (Table I). The proportion of patients with elevated PCWP and 2R/3R rejection was 9.3% (4/43). There was no difference between patients with normal or elevated PCWP regarding mild rejection (1R) at the time of investigation or history of previous 1R or 2R/3R rejection. Pathological findings at coronary angiography were more common in patients with elevated PCWP. Patients with elevated PCWP had more severe pulmonary hypertension but no difference in cardiac index or pulmonary vascular resistance (Table I). Patients with elevated PCWP had lower blood pressure and higher heart rate compared with normal PCWP. Patients with elevated PCWP had significantly more severe tricuspid (Grade 3), reduced RV fraction area change and more severe mitral regurgitation (Grade 3 and Grade 2) (Table I). Elevated PCWP were most common within the first month and when RHC was performed more than 12 months following transplantation (Table II).

Relationship of Right- and Left-Sided Filling Pressures:

The RAP was not measured in one of the subjects. The RAP was elevated in 45% (50/112, mean RAP>8 mmHg) of the investigations. The PCWP was elevated in 38% (43/113, mean PCWP>15 mmHg) of the investigations. The linear relation between catheter PCWP and catheter RAP was strong (R = 0.88, Fig. 1 left). The catheter PCWP was with few exceptions higher than the catheter RAP (Fig., 1 right). Both the RAP and PCWP were normal in 51.8% (58/112) and both elevated in 34.8% (39/112), yielding a concordance rate of 86.6% (kappa 0.73, 95% CI 0.60–0.85). Similar concordance rate was observed in patients investigated <3 months (n = 26, concordance rate 84.6%, kappa 0.69, 95% CI 0.41–0.97) and >12 months (n = 23, concordance rate 82.6%, kappa 0.62, 95% CI 0.28–0.96) following transplantation. Elevated RAP with normal PCWP was a more common finding than normal RAP with elevated PCWP. The linear relation between echo and catheter RAP was strong (Spearman's rho = 0.74, P < 0.0001). There was a significant difference with underestimation of RAP by echo but in

TABLE I

Clinical, Echocardiographic, and Right Heart Catheterization Data

	PCWP ≤ 15 mm Hg (n = 70)	PCWP > 15 mm Hg (n = 43)	P-Value
Age (years)	37 ± 12	35 ± 15	0.34
Male gender (%)	75	80	0.62
Donor age (years)	36 ± 8	34 ± 10	0.44
BSA (m^2)	1.74 ± 0.23	1.80 ± 0.23	0.31
Systolic blood pressure (mmHg)	126 ± 20	114 ± 22	0.005
Diastolic blood pressure (mmHg)	79 ± 14	70 ± 16	0.005
Heart rate (bpm)	90 ± 12	97 ± 15	0.01
Creatinin	106 ± 39	99 ± 36	0.18
Days between THx and RHC	241 (105–347)	211 (50–586)	1.00
Rejection 1R (%)	34	41	0.54
Rejection 2R/3R (number)	0/0	3/1	0.018
Previous 1R rejections (number)	178	103	0.55
Previous 2R/3R rejections (number)	16	18	0.23
Humoral (number)	1	2	0.56
TR Grade 3 (number)	1	7	0.005
MR Grade 3/Grade 2 (number)	0/0	1/5	0.002
RV end diastolic area (cm^2)	16.0 ± 3.0	16.1 ± 3.5	0.88
RV fractional area change (%)	43.0 ± 8.7	34.5 ± 11.7	<0.0001
Coronary artery disease (%)	4.3	47	0.003
Mean RAP (mmHg)	5 (3–8)	16 (11–20)	<0.0001
PASP (mmHg)	31 ± 5.4	45 ± 7.8	<0.0001
PAMP (mmHg)	21 ± 4.2	32 ± 5.6	<0.0001
Mean PCWP (mmHg)	10 (8–13)	22 (19–26)	<0.0001
CI (L/min per m^2)	2.9 ± 0.8	2.7 ± 0.7	0.29
PVR (Wood units)	1.9 (1.4–2.7)	1.7 (1.3–2.6)	0.20

Data are presented as mean ± SD or median (25 and 75 percentile) when appropriate. BSA = body surface area; THx = transplantation; RHC = right heart catheterization; TR = tricuspid regurgitation; MR = mitral regurgitation; RAP = right atrial pressure; PASP = pulmonary artery systolic pressure; PAMP = pulmonary artery mean pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; PVR = pulmonary vascular resistance; RV = right ventricle.

TABLE II

The Effect of Time after Transplantation on the Occurrence of Elevated RAP and PCWP

					Post Hoc Analysis		
	Group 1 0–1 Months	Group 2 2–12 Months	Group 3 >12 Months	Overall P-Value	Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
RAP>8 mmHg, % (n)	73 (15)	32 (74)	65 (23)	0.025	0.007	0.73	0.007
PCWP>15 mmHg, % (n)	60 (15)	25 (75)	65 (23)	0.008	0.013	1.0	0.0009

Group 1 constitutes patients investigated within the first month, Group 2 patients investigated within the second and 12th month, and Group 3 more than 12 months after transplantation. RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure.

absolute terms the mean difference was small (1 ± 4.3 mmHg, P = 0.02).

Increased PCWP by Echocardiography:
Patients with elevated PCWP had lower LV ejection fraction, larger left ventricular diastolic volumes, and increased wall thickness as compared to those with normal PCWP (Table III). Additionally they had lower pulmonary vein S/D ratio, higher mitral E/A ratio, shorter E-wave deceleration time, and shorter IVRT compared to those with normal PCWP. The septal, lateral, and average E/E′ were significantly higher in patients with elevated PCWP compared to those with normal PCWP (Table III). The patients with elevated PCWP had significantly higher RAP by echocardiography, wider IVC diameter, and lower caval index compared to patients with normal PCWP.

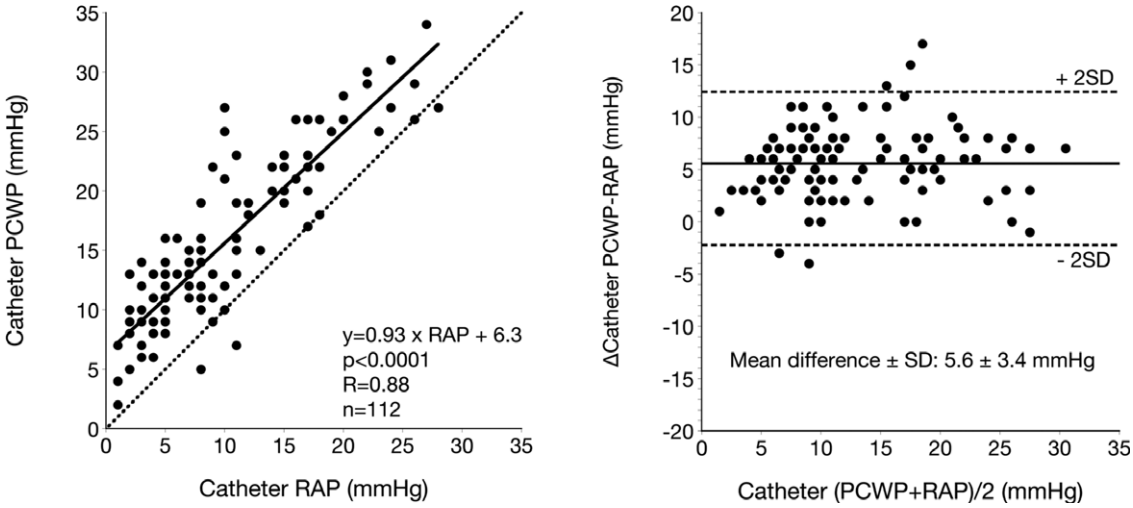

Figure 1. Scatter plots that show the linear relation (left) and Bland-Altman plot for catheter RAP and catheter PCWP. RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure.

The estimated RAP was increased (≥10 mmg) in 10% (7/70) of patients with normal PCWP and in 81% (35/43) in patients with elevated PCWP.

The linear relation between catheter PCWP and E/A, S/D, DT, IVRT, lateral wall E/E′, and PASP was weak to moderate (Fig. 2). The corresponding relation was moderate to strong for IVC maximum diameter, estimated RAP and the caval index with correlation coefficients 0.61 ($P < 0.0001$), 0.69 ($P < 0.0001$), and 0.72 ($P < 0.0001$). Patients investigated with echocardiography and RHC at the same day had the same degree of linear relation

TABLE III

Echocardiography Data for Assessment of Pulmonary Capillary Wedge Pressure

	PCWP ≤15 mmHg (n = 70)	PCWP >15 mmHg (n = 43)	P-Value
LV ejection fraction	59 ± 8	53 ± 13	0.004
IVS thickness (mm)	8.8 ± 1.3	9.2 ± 1.6	0.13
PW thickness (mm)	8.1 ± 1.0	8.5 ± 1.3	0.043
LV diastolic volume (mL)	73 ± 15	80 ± 21	0.05
Left atrial volume index (mL/m^2)	39 ± 14	55 ± 24	<0.0001
Pulmonary vein S (cm/sec)	30 ± 9	29 ± 15	0.73
Pulmonary vein D (cm/sec)	48 ± 13	56 ± 17	0.006
S/D ratio	1.0 (0–1.0)	0.5 (0–1.0)	0.04
Mitral E velocity (cm/sec)	80 ± 22	103 ± 19	<0.0001
Mitral A velocity (cm/sec)	38 ± 11	37 ± 19	0.60
Mitral E/A	2.2 ± 0.7	3.1 ± 0.9	<0.0001
Deceleration time (ms)	158 ± 37	112 ± 39	<0.0001
Isovolumic relaxation time (ms)	82 ± 15	63 ± 19	<0.0001
Mitral A duration (ms)	116 ± 16	108 ± 25	0.13
Tissue E′ septum (cm/sec)	7.8 ± 2.3	7.3 ± 2.2	0.39
Tissue A′ septum (cm/sec)	6.1 ± 1.7	5.0 ± 2.7	0.02
Tissue E′ lateral (cm/sec)	11.9 ± 3.6	10 ± 3.3	0.006
Tissue A′ lateral(cm/sec)	6.3 ± 2.1	5.3 ± 2.9	0.04
E/E′ septum	11.1 ± 4.4	15.6 ± 5.9	<0.0001
E/E′ lateral	7.3 ± 3.0	11.7 ± 5.6	<0.0001
E/E′ average	9.3 ± 3.4	13.6 ± 5.2	<0.0001
Right atrial pressure (mmHg)	5 (5–5)	15 (5–20)	<0.0001
IVC maximum diameter (mm)	13 ± 6.3	23 ± 5.6	<0.0001
Caval index (%)	80 (56–100)	23 (0–44)	<0.0001
Doppler PASP (mmHg)	28 ± 6.2	40 ± 9.6	<0.0001

Data are presented as mean ±SD or median (25 and 75 percentile) when appropriate. LV = left ventricular; IVS = interventricular septum; PW = posterior wall; LV = left ventricular; IVC = inferior vena cava; PASP = pulmonary artery systolic pressure.

as those investigated with echocardiography either the day before or the day following RHC.

Figure 3 shows the ROC curves for the detection of increased PCWP from the derivation group with mitral inflow, tissue Doppler parameters and Doppler PASP (left), and IVC parameters (right). The areas under the curve were largest for the IVC parameters and Doppler PASP. Table IV shows the diagnostic performance in the test population using cutoff values from the derivation group.

Discussion:

In this study of HTx recipients, we found that echocardiography can be used to assess left-sided filling pressures.

Only few studies have been done in HTx recipients with relatively small number of patients that explored left-sided or right-sided filling pressures.[7–9] Our findings regarding the mitral inflow parameters (E/A, DT, and IVRT) and the strength of their relation to PCWP are in agreement with some[8] but not with others that found weaker correlations.[7,9] Sundereswaran et al. found that tissue Doppler in combination with mitral early diastolic flow was superior to the mitral inflow parameters alone and could be used to predict elevated PCWP. The relation between mean PCWP and E/E′ in their study was strong (R = 0.80) compared with the moderate relation observed in our study (R = 0.52). We did not as they did, perform echocardiography and RHC investigations simultaneously but analyzing patients investigated within the same day did not improve the degree of linear relation. The marked difference in performance between the two studies using tissue Doppler parameters questions the usefulness of this method in predicting elevated PCWP in HTx recipients and our findings are supported by others.[9] All the HTx recipients were operated with the bicaval method. This improves the atrial function[14] compared with the previous standard technique but still in transplanted hearts we can expect atrial contractile dysfunction. This can be seen as low or varying A-wave velocities causing increased E/A ratio and mimics restrictive physiology but does not necessarily reflect high filling pressure. The mitral inflow parameters are most useful in combination with tissue Doppler and Doppler PASP. Elevated PCWP can be ruled in if three of total five (E/A, DT, IVRT, E/E′ lateral, and Doppler PASP) parameters are positive. The sensitivity for these parameters alone is relatively low, however, elevated PCWP is unlikely if none of the five parameters reach cutoff values.

Several studies have documented the ability of echocardiographic parameters to assess mean

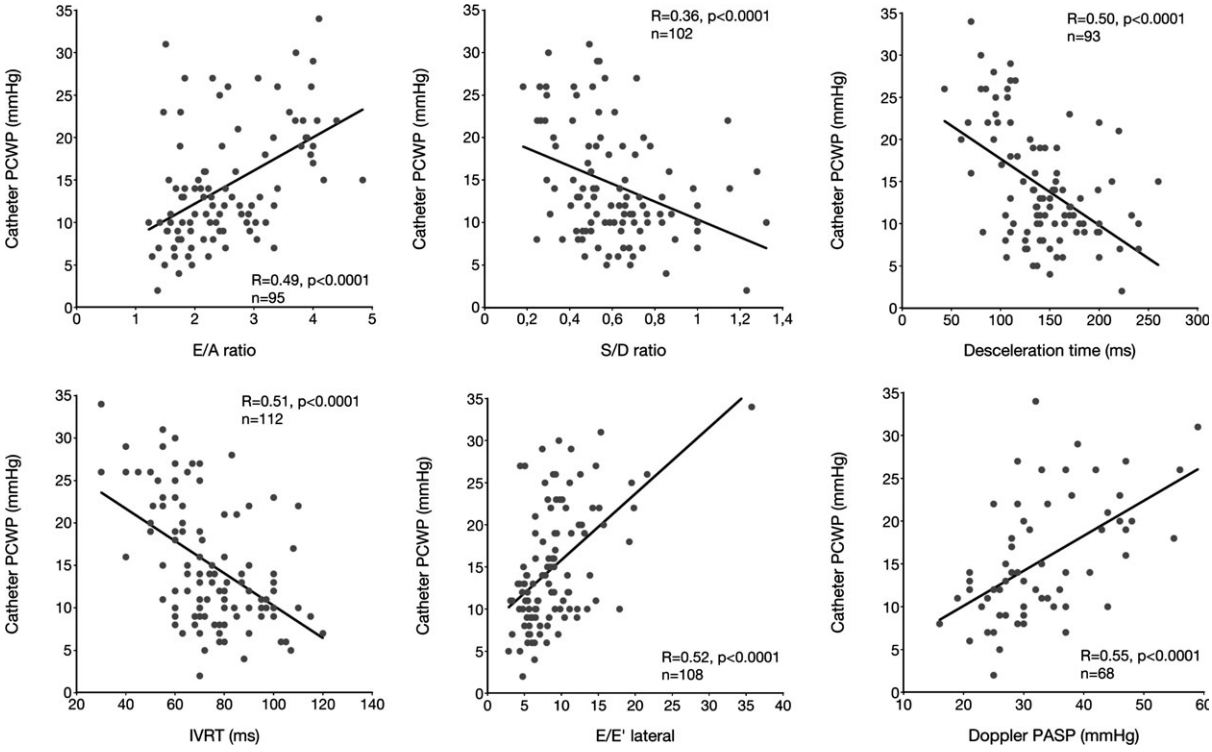

Figure 2. Scatter plots that show the linear relation between catheter PCWP and mitral inflow, tissue Doppler, and Doppler PASP data. PCWP = pulmonary capillary wedge pressure; PASP = pulmonary artery systolic pressure.

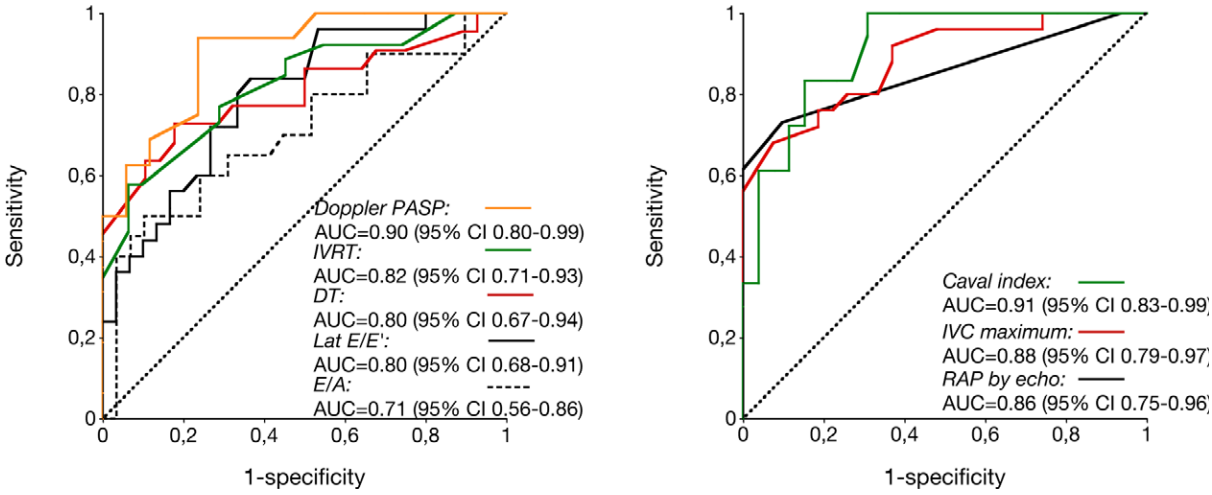

Figure 3. Receiver operating characteristic curves from the derivation group (n = 56) for the detection of elevated PCWP (>15 mmHg) for mitral inflow, tissue Doppler (left), and IVC (right) parameters. The full color figure is available in the online version of this article. PCWP = pulmonary capillary wedge pressure; IVC = inferior vena cava.

TABLE IV

Diagnostic Performance Regarding Assessment of Elevated Pulmonary Capillary Wedge Pressure (>15 mmHg)

Variable	n	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Diagnostic Odds Ratio (95% CI)
IVC parameters							
IVC max (mm)	54	>19	82 (59–94)	95 (82–99)	15.3 (3.9–60)	0.19 (0.07–0.52)	82 (12.3–542)
Echo RAP (mmHg)	56	>5	94 (73–99)	90 (76–96)	9.2 (3.4–23)	0.07 (0.01–0.44)	140 (14–1355)
Caval index	47	<43	92 (67–19)	91 (77–97)	10.5 (3.5–31)	0.08 (0.01–0.55)	124 (12–1321)
Spectral and tissue Doppler parameters							
E/A	46	>3.1	75 (47–91)	89 (74–95)	6.6 (2.5–17.5)	0.28 (0.1–0.76)	23 (4.4–123)
DT	49	<120	82 (52–95)	86 (73–94)	6.2 (2.6–14.8)	0.21 (0.06–0.74)	29.7 (4.9–179)
IVRT	56	<65	65 (41–83)	87 (73–94)	5.0 (2.1–12.3)	0.41 (0.21–0.78)	12.5 (3.2–49)
E/E′ lateral	55	>12	38 (18–61)	89 (76–96)	3.6 (1.2–10.9)	0.70 (0.47–1.0)	5.1 (1.2–22)
Doppler PASP	34	>36	70 (40–89)	83 (64–93)	4.2 (1.6–11.2)	0.36 (0.13–0.94)	11.7 (2.1–66)
One positive	56		94 (73–99)	62 (46–75)	2.4 (1.6–3.7)	0.09 (0.01–0.65)	25.6 (3.1–213)
Two positive	56		76 (53–90)	85 (70–93)	5.0 (2.3–10.9)	0.28 (0.12–0.66)	17.9 (4.3–74)
Three positive	50		50 (25–75)	94 (82–98)	9 (2.1–39)	0.53 (0.30–0.9)	17 (2.8–105)

IVC = inferior vena cava; RAP = right atrial pressure; DT, deceleration time; IVRT = isovolumic relaxation time; PASP = pulmonary artery systolic pressure.

RAP in patients with various cardiac disorders.[11,12,15–18] Inspection of the IVC with measurement of the diameter and the effect of breathing or sniffing (collapsibility) is the method that is most thoroughly studied,[11,12,15–17] and has gained the most widespread use. In this study, we found a high degree of concordance between right- and left-sided filling pressures in HTx recipients. It is well known from invasive studies done in heart failure patients that the filling pressures in the ventricles are often simultaneously elevated. This concordance has been studied in patients with normal[19] and depressed left ventricular systolic function.[19,20] The concordance rates (low RAP and low PCWP, elevated RAP and elevated PCWP) are in the range of 72–79% and this encourages the use of bedside assessment of jugular venous pressure as a surrogate for PCWP.[21] The degree of concordance in our study population was even higher than in patients with severe heart failure.[19,20] We can only speculate regarding the explanation for this high degree of concordance. Within the first month following HTx, there is a tendency to accumulate fluid due to a systemic inflammatory response and the early high doses of corticosteroids used. The elevated filling pressures, therefore, might reflect volume status, however, the

high degree of concordance was also observed in patients investigated >12 months following transplantation. In the early stage, this can also be due to mismatch between donor and recipient body size and the effect of donor organ ischemia causing restrictive physiology in both ventricles.[3] The simultaneous increase in RAP and PCWP observed later is most likely due to some degree of restrictive myocardial process involving both ventricles simultaneously. The high degree of concordance between right- and left-sided filling pressures is useful because when observed on the right side by echocardiography it indicates increased PCWP. However, we should use this with caution. Increased PCWP does not necessarily mean increased RAP and vice versa. The assessment of normal or elevated PCWP should be supported by the mitral inflow (E/A, DT, IVRT), tissue Doppler, and Doppler PASP findings. The presence of cutoff values in mitral inflow parameters increases the likelihood of elevated PCWP significantly with high positive likelihood ratios. The absence of individual cutoff values for mitral inflow does not reduce the likelihood of elevated PCWP importantly. However, if the patient does not have any mitral inflow, tissue Doppler or Doppler PASP cutoff values present the likelihood of elevated PCWP is markedly reduced (negative likelihood ratio 0.09). The presence of three or more cutoff values for these parameters increases the likelihood of elevated PCWP to a large extent (positive likelihood ratio 9).

Cardiac allograft vasculopathy might occur early[22] and cause restrictive physiology[23] but generally it is a disease that develops over time and only a minority of our patients were investigated more than 1 year following HTx. Coronary angiogram data were present in 40% of the patients included. Pathological findings indicating cardiac allograft vasculopathy were a frequent finding in these patients (25%) and significantly related to elevated PCWP. Patients with acute cellular rejection (2R, 3R) are known to have restrictive physiology[24] and indeed all patients with acute cellular 2R/3R or humoral rejection had increased PCWP. However, rejection of this degree was an uncommon finding (n = 7), and therefore we cannot evaluate the ability of echocardiography to rule in or rule out rejection based on filling pressure. The elevated PCWP observed could only partly be explained by rejection or allograft vasculopathy. Recent studies using cardiac magnetic resonance imaging and gadolinium contrast have demonstrated fibrosis with typical infarct location explained by allograft vasculopathy.[25,26] Interestingly, in a large proportion of HTx recipients an atypical pattern of fibrosis was observed that could not be explained by allograft vasculopathy.[25,26] Further studies are needed to investigate the incidence of diastolic dysfunction in HTx recipients not related to acute allograft rejection or vasculopathy, its causes, natural history and prognostic importance.

The clinical implications of the study are twofold. First, the presence of elevated PCWP is a common finding in HTx recipients undergoing routine endomyocardial biopsies. Only a small proportion of them will have a more severe rejection (2R, 3R) and among HTx recipients with severe rejection normal PCWP is a common finding.[27] We can conclude that the role of assessment of filling pressure in a transplanted heart is limited regarding detect rejection. There are some reports[27,28] on the use of myocardial deformation imaging that are promising but still echocardiography cannot replace endomyocardial biopsies for surveillance of rejection.[29] Second, the easily obtained echocardiographic assessment of filling pressures could help the clinician to adjust diuretics that are commonly used in HTx recipients, especially in the first year post transplant until the heart fully recovers.

Study Limitations:

The major limitations of this study are related to the retrospective design and that echocardiography and RHC were not performed simultaneously. The patients were fasting and without intravenous fluid administration during or following the RHC procedure. A majority of the echocardiography investigations were done with a nonfasting patient and this might have introduced a bias of higher RAP compared with at RHC. In a previous study, we evaluated the relationship between catheter and echocardiography RAP in both the simultaneous and nonsimultaneous setting. The relationship was strongest with simultaneous investigations (R = 0.88) but also the nonsimultaneous relationship was strong (R = 0.82).[30] Importantly, the nonsimultaneous design should not be in favor of echocardiography and give a false impression of good diagnostic performance. RHC is the golden standard, however, the invasive measurements of RAP and PCWP[31] are known to introduce errors. Some of the diagnostic discrepancies might, therefore, be due to errors in these invasive measurements. The assessment of RAP from inspection of the IVC was possible in all patients and there were no missing spectral or tissue Doppler data. It was, however, not possible to calculate the caval index in all patients due to limitations in the digital documentation and difficult to know if the sniffing procedure to evaluate collapsibility was performed properly. This may lead to an erroneous assessment of elevated RAP by echocardiography. In recent recommendations on how to assess diastolic function different algorithms are

used for patients with normal versus reduced systolic function.[10] This might be the case also with HTx recipients but due to a small number with LVEF <50% (21%) this could not be further analyzed. We do not present data on the duration of organ ischemia prior to transplantation and the occurrence of treatment for hypertension. These data could have been of value to elucidate possible contributors to the hemodynamics observed.

Conclusions:

We found that echocardiography can be used to assess left-sided filling pressures in HTx recipients. The most reliable parameters for the assessment of PCWP are those related to elevated RAP. This is explained by the observation that there is a high degree of concordance between right- and left-sided filling pressures in HTx recipients.

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