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RESEARCH ARTICLE

Cardiac output states in patients with severe functional tricuspid regurgitation: impact on treatment success and prognosis

Matthias Unterhuber[1†]**, Karl-Patrik Kresoja**[1†]**, Christian Besler**[1]**,
Karl-Philipp Rommel**[1]**, Mathias Orban**[2,3]**, Maximilian von Roeder**[1]**, Daniel Braun**[2,3]**,
Lukas Stolz**[2,3]**, Steffen Massberg**[2,3]**, Jonel Trebicka**[4]**, Markus Zachäus**[5]**,
Jörg Hausleiter**[2,3]**, Holger Thiele**[1‡]**, and Philipp Lurz**[1*‡]

[1]Department of Cardiology, Heart Center Leipzig at University of Leipzig, Leipzig, Germany; [2]Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Munich, Germany; [3]Munich Heart Alliance, Partner site German Centre for Cardiovascular Research (DZHK), Berlin, Germany; [4]Translational Hepatology, Department of Internal Medicine I, Goethe University Clinic Frankfurt, Frankfurt, Germany; and [5]Department of Gastroenterology, Hepatology, Hematology and Oncology, Helios Park-Klinikum Leipzig, Leipzig, Germany

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Aims	To investigate whether there is evidence for distinct cardiac output (CO) based phenotypes in patients with chronic right heart failure associated with severe tricuspid regurgitation (TR) and to characterize their impact on TR treatment and outcome.
Methods and results	A total of 132 patients underwent isolated transcatheter tricuspid valve repair (TTVR) for functional TR at two centres. Patients were clustered according to k-means clustering into low [cardiac index (CI) < 1.7 L/min/m^2], intermediate (CI $1.7-2.6$ L/min/m^2) and high CO (CI > 2.6 L/min/m^2) clusters. All-cause mortality and clinical characteristics during follow-up were compared among different CO clusters. Mortality rates were highest for patients in a low (24%) and high CO state (42%, log-rank $P < 0.001$). High CO state patients were characterized by larger inferior vena cava diameters ($P = 0.003$), reduced liver function, higher incidence of ascites ($P = 0.006$) and markedly reduced systemic vascular resistance ($P < 0.001$) as compared to TTVR patients in other CO states. Despite comparable procedural success rates, the extent of changes in right atrial pressures ($P = 0.01$) and right ventricular dimensions ($P < 0.001$) per decrease in regurgitant volume following TTVR was less pronounced in high CO state patients as compared to other CO states. Successful TTVR was associated with the smallest prognostic benefit among low and high CO state patients.
Conclusions	Patients with chronic right heart failure and severe TR display distinct CO states. The high CO state is characterized by advanced congestive hepatopathy, a substantial decrease in peripheral vascular tone, a lack of response of central venous pressures to TR reduction, and worse prognosis. These data are relevant to the pathophysiological understanding and management of this important clinical syndrome.

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*Corresponding author. Department of Internal Medicine/Cardiology, Heart Center Leipzig at University of Leipzig, Strümpellstraße 39, 04289 Leipzig, Germany. Tel: +49 341 8651428, Fax: +49 341 865-1461, Email: philipp.lurz@medizin.uni-leipzig.de

†Both authors contributed equally and should be considered as shared first authors.
‡Both authors contributed equally and should be considered as shared last authors.

Graphical Abstract
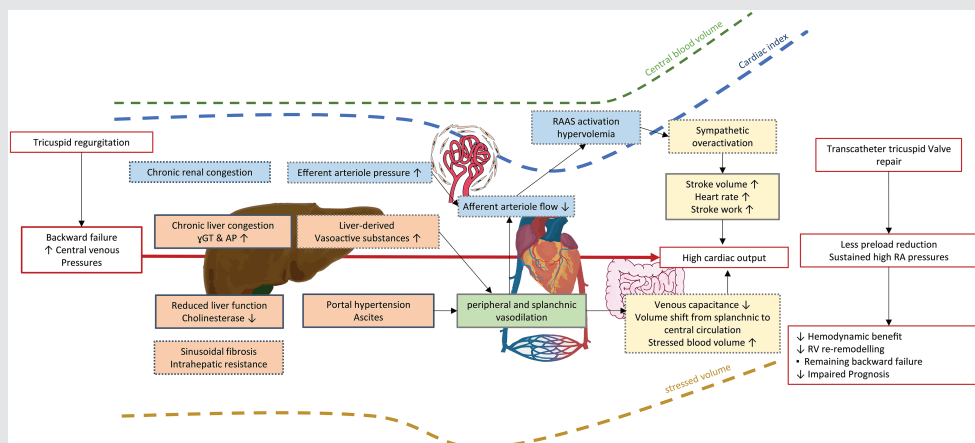
Proposed mechanism of hypercirculatory tricuspid regurgitation. Tricuspid regurgitation related backward failure causes liver congestion and dysfunction with portal hypertension and reduced washout of vasoactive substances. Consequent splanchnic and peripheral vasodilatation alongside with reduced renal blood flow results in renin−angiotensin−aldosterone system (RAAS) activation and sympathetic overactivation. The sympathetic drive and volume retention lead to further capacitance depletion and volume overload, eventually resulting in a high cardiac output state, with limited preload reduction and prognostic benefit following transcatheter tricuspid valve repair. The alterations in the graph should be interpreted as simultaneous interaction rather than a timeline. Continuous lines indicate findings in the present study. Dashed lines express currently accepted mechanistical considerations. AP, alkaline phosphatase; γGT, gamma-glutamyl-transferase; RA, right atrium; RV, right ventricle.

Introduction

Severe tricuspid regurgitation (TR) is increasingly recognized as an important determinant of functional status and prognosis in different aetiologies of heart failure.[1] Functional TR is frequently asymptomatic in the early stages, patients with this lesion often present late in the course of the disease with profound remodelling of the right heart chambers, massive or torrential TR grades, and long-standing venous congestion.[2] Indeed, poor outcomes of tricuspid valve surgery have recently been suggested as a result of late referral, given that a substantial number of patients are referred with decompensated heart failure, advanced liver disease and previous unplanned hospitalizations.[3]

Transcatheter tricuspid valve repair (TTVR) is currently evaluated as an alternative therapeutic option to address the symptomatic burden and poor outcome in patients with functional TR at increased surgical risk. While accumulating evidence suggests that functional TR can be safely treated by TTVR and various predictors of device and patient success have been identified,[4–8] the individual clinical benefit derived from the procedure is still hard to estimate. This may, at least in part, be related to the fact that the pathophysiological implications of long-standing TR as well as its treatment in chronic right heart failure in the adult patient are largely unknown, particularly on an extracardiac level.

Despite recent efforts to define the natural history of TR by echocardiographic or cardiac magnetic resonance imaging,[9,10] the unique systemic haemodynamic changes in patients with symptoms of right heart failure and severe TR remain to be defined. Therefore, to improve our understanding of the interaction between cardiac output (CO), chronic venous congestion and hepatorenal function, the present study sought to characterize CO state phenotypes among patients with chronic right heart failure complicated by severe TR and investigates their relevance for TTVR.

Methods

Study population

For this analysis, consecutive patients with severe symptomatic functional TR undergoing isolated TTVR using the MitraClip™ (Abbott Vascular, Santa Clara, CA, USA) or PASCAL (Edwards Lifesciences, Irvine, CA, USA) device at two German tertiary care centres between 2016 and 2019 were included. Patients were excluded if they had failure to deploy at least one device or in case of missing invasive cardiac index (CI) measurements at baseline. Pre-procedural assessment included a comprehensive transthoracic and transoesophageal echocardiography, evaluation of laboratory parameters such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Cobas, Elecsys NT-proBNP II, Roche, Basel, Switzerland), creatinine, estimated glomerular filtration

rate (eGFR), glutamic oxaloacetic transaminase, glutamate-pyruvate transaminase, gamma-glutamyl transferase (GGT), bilirubin, alkaline phosphatase and cholinesterase levels. Echocardiographic assessment was performed as previously described.[6] In brief, grading of TR severity was based on the assessment of vena contracta, effective regurgitant orifice area (EROA) and estimated regurgitant volume according to proximal isovelocity surface area. TR severity grades of mild, moderate, and severe were extended by a grade IV (massive or torrential).[11] Inferior vena cava diameters were assessed in a standardized fashion. All patients were discussed in the local interdisciplinary heart team meeting prior to TTVR and considered to be at high or prohibitive risk for surgery. This retrospective analysis was approved by the local ethics committee and all patients gave written informed consent for the procedure. The study cohort and the investigation conform with the principles outlined in the Declaration of Helsinki.

Cardiac output measurement and haemodynamic assessment

Echocardiographically estimated CO was measured by multiplying heart rate with the stroke volume derived from the velocity-time integral and diameter of the left ventricular outflow tract (LVOT) from pre-procedural transthoracic echocardiography. Mean values of three consecutive beat measurements were used if patients were in sinus rhythm and if patients were in atrial fibrillation; at least five consecutive beats were used for heart rate assessment and velocity-time integral assessment. Lastly, it was divided by body surface area to derive CI.

In order to validate echocardiographically estimated CI, all patients underwent pre-procedural haemodynamic evaluation by right heart catheterization in median 1 day before TTVR. Invasive CI was measured by Fick's formula or thermodilution, according to the operator's discretion. Pulmonary capillary wedge pressure, systolic pulmonary pressure, diastolic pulmonary artery pressure, mean pulmonary artery pressure and right atrial pressure (RAP) were assessed.

Transcatheter tricuspid valve repair

Transcatheter tricuspid valve repair was performed under general anaesthesia with interventional guidance by transoesophageal echocardiography and fluoroscopy via the right femoral vein. Transcatheter edge-to-edge repair was carried out either with the MitraClip (Abbott Vascular, Santa Clara, CA, USA) or PASCAL system (Edwards Lifesciences, Irvine, CA, USA), as described previously.[12,13] Echocardiographic multiplane imaging, including transgastric views, was used to guide and confirm correct device position and leaflet grasping. Intraprocedural RAP was measured under general anaesthesia after advancing the device into the right atrium and after deployment of the last device.

Follow-up examinations

Patients underwent a thorough physical examination and transthoracic echocardiography assessment at discharge and at 1-, 6- and 12-month follow-up visits. Patients were regularly contacted by telephone if no further outpatient appointments were scheduled.

Outcomes

Procedural success of TTVR was defined as successful device placement and reduction of TR by at least one grade as assessed on transthoracic echocardiography at discharge.

The primary outcome was all-cause death within 1 year after the index procedure. Secondary endpoints were the incidence of first heart failure hospitalization, a combined endpoint of heart failure hospitalization or death; changes in New York Heart Association (NYHA) functional class, echocardiographic right ventricular dimensions and inferior vena cava, RAP and NT-proBNP levels at last available follow-up were explored.

Statistical analysis

Normal distribution was tested using Shapiro−Wilk tests. Parametric data are given as their mean and corresponding standard deviation; in case of non-parametric distribution data are given as median and corresponding interquartile range (IQR). ANOVAs or Kruskal−Wallis tests were used to compare continuous variables. Categorical variables were compared with Chi^2 tests and, if appropriate, *P* for trend is displayed.

We performed a Bland−Altman plot analysis to assess differences in echocardiography and invasively derived CI and assessed interobserver variability of the echocardiographic measurements by two external operators, therefore calculating a two-way mixed-effects model with intra-class correlation coefficients.

To find the optimal number of groups (clusters) to yield the highest between-group differences, an analysis using k-means statistics was performed. Namely, to estimate the best cluster number for the interaction of echocardiographically derived CI and the primary outcome, k-means statistics were calculated by computing reiterated k-means for a range of k values to generate clusters with high intra-class similarity and low inter-class similarity (i.e. low and high variances, respectively). A graphical analysis yielded a cluster number of k = 3 as best match for high intra-cluster similarity and low inter-cluster similarity to allow for accurate characterization of the groups. These clusters were named by their principal characteristics in low (CI < 1.7 L/min/m^2), intermediate (CI 1.7−2.6 L/min/m^2) and high CO (CI > 2.6 L/min/m^2) phenotypes. Kaplan−Meier analyses were used to compare the survival in different subgroups; log-rank tests were used to test for differences. The prognostic relevance of dichotomous variables with regard to the primary outcome was assessed using logistic regression analyses; results were plotted and explored using 'ggiraphExtra' and 'plotly' packages for R. Results are presented as odds ratios with corresponding 95% confidence intervals. Cox regression analyses were performed to test the prognostic relevance of dichotomous and continuous variables with regard to the primary outcome; results are presented as hazard ratios with corresponding 95% confidence intervals.

The underlying assumptions of the statistical tests were evaluated. A two-sided significance level of α 0.05 was defined appropriate to indicate statistical significance. Statistical analyses were performed using R (version 4.0.3) and figures were illustrated using GraphPad Prism (version 8.4.0 for MacOS, GraphPad Software, La Jolla, CA, USA).

Results

Cohort description

Overall, 170 patients with severe or massive/torrential functional TR and symptoms of right heart failure scheduled for isolated TTVR between 2016 and 2019 were considered for the present analysis. Patients were excluded for missing CI measurements during catheterization prior to the procedure (n = 24), chronic dialysis (n = 8), or failure to deploy at least one device during TTVR (n = 6), leaving a cohort of 132 patients included in the present analysis.

Table 1 Baseline characteristics

	All patients	Low cardiac output state (CI <1.7 L/min/m^2)	Intermediate cardiac output state (CI 1.7–2.6 L/min/m^2)	High cardiac output state (CI >2.6 L/min/m^2)	P-value
Patients, n	132	33	73	26	
Age, years	76 (± 9)	77 (± 6)	77 (± 10)	72 (± 11)	0.050
Female sex, n (%)	50 (38)	27 (82)	42 (58)	13 (50)	0.021
BMI, kg/m^2	25.7 (23–29)	26 (23–31)	26 (23–28)	25 (23–28)	0.84
BSA, m^2	1.80 (1.73–1.98)	1.74 (1.73–1.89)	1.85 (1.73–1.98)	1.83 (1.73–2.01)	0.35
EuroSCORE II, %	5.3 (3.3–9.6)	5.8 (4–10)	4.6 (3–9)	5.3 (3–10)	0.56
Atrial fibrillation, n (%)	104 (79)	28 (85)	57 (78)	19 (73)	0.39
Beta-blocker treatment, n (%)	123 (93)	33 (100)	66 (90)	24 (92)	0.16
Sacubitril/valsartan treatment, n (%)	1 (1)	0	0	1 (4)	0.20
Arterial hypertension, n (%)	126 (95)	33 (100)	68 (93)	25 (96)	0.39
Chronic lung disease, n (%)	29 (22)	10 (30)	13 (19)	6 (23)	0.35
Previous left valvular surgery, n (%)	14 (11)	2 (6)	6 (8)	6 (23)	0.10
Previous clip in mitral position, n (%)	14 (11)	4 (12)	6 (8)	4 (15)	0.48
RV lead, n (%)	34 (26)	8 (24)	19 (26)	7 (27)	0.97
CRT-D system, n (%)	2 (2)	1 (3)	1 (1)	0	0.70
History of CABG, n (%)	20 (15)	5 (15)	11 (15)	4 (15)	0.99
NYHA class, n (%)					0.52
II	18 (14)	4 (12)	13 (18)	1 (3.8)	
III	86 (65)	22 (67)	45 (62)	19 (73)	
IV	28 (21)	7 (21)	15 (21)	6 (23)	
Oedema, n (%)	95 (72)	20 (61)	55 (75)	20 (77)	0.24
Ascites, n (%)	30 (23)	5 (15)	13 (18)	12 (46)*	0.006
Child-Pugh grade, n (%)					0.031
A	96 (73)	25 (76)	58 (79)	13 (50)	
B	23 (17)	5 (15)	10 (14)	8 (31)	
C	13 (10)	3 (9)	5 (7)	5 (19)	
Laboratory results					
Alkaline phosphatase, μ/L	102 (73–146)	105 (69–157)	89 (72–124)	133 (96–180)*	0.018
GGT, u/L	101 (71–196)	89 (59–167)	108 (75–199)	117 (83–268)*	0.050
Cholinesterase, μ/L	5.36 (± 1.85)	5.8 (± 2)	5.6 (± 2)	4.1 (± 1)*	0.008
Bilirubin total, mg/dL	1.40 (1.02–1.79)	1.5 (1–2)	1.5 (1–2)	1.2 (1–2)	0.12
GOT, μ/L	28 (23–38)	30 (23–38)	28 (23–37)	32 (23–39)	0.72
GPT, μ/L	20 (14–26)	22 (17–30)	20 (13–25)	19 (13–26)	0.17
eGFR, mL/min/1.73 m^2	59 (33–62)	63 (47–71)	53 (36–68)	54 (39–77)	0.35
<30 mL/min/1.73 m^2	22 (17)	4 (12)	13 (18)	5 (19)	0.64
Haemoglobin, mmol/L	8.00 (7.19–8.82)	8.20 (7.20–8.72)	7.80 (7.00–8.90)	8.07 (7.45–8.52)	0.65
NT-proBNP, ng/L	2657 (1384–5103)	3038 (1718–5226)	2512 (1418–5482)	2438 (878–4090)	0.34

BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CI, cardiac index; CRT-D, cardiac resynchronization therapy with defibrillator; eGFR, estimated glomerular filtration rate; GGT, gamma−glutamyl transferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamate-pyruvate transaminase; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RV, right ventricular.
*Indicates a level of significance of $P < 0.05$ between low and high cardiac output state.

Patients were at advanced age and highly symptomatic for severe or massive/torrential TR with 86% (n = 114) presenting in NYHA class III or IV. More than two thirds displayed peripheral oedema and ascites was evident in 23% of the patients (*Table 1*). Based on pre-procedural echocardiography, 112 (85%) had severe and 20 (15%) massive/torrential TR. Patients presented with right ventricular dilatation [median midventricular right ventricular diameter 43 (IQR 39−48) mm], and impaired right ventricular systolic function according to tricuspid annular plane systolic excursion <17 mm was present in 51% of cases (*Table 2*). Concomitant to an elevated RAP, the diameter of the inferior vena cava was markedly dilated and laboratory parameters displayed evidence of congestive hepatopathy.

Quantification of cardiac index and cardiac index-based phenotyping of severe tricuspid regurgitation

Left ventricular outflow tract-based stroke volume calculations on echocardiography revealed a CI of 2.20 (IQR 1.75−2.60) L/min/m^2.

Table 2 Echocardiographic and haemodynamic characteristics

	All patients	Low cardiac output state (CI <1.7 L/min/m^2)	Intermediate cardiac output state (CI 1.7–2.6 L/min/m^2)	High cardiac output state (CI >2.6 L/min/m^2)	P-value
Patients, *n*	132	33	73	26	
Echocardiography					
CI, mL/min/m^2	2.20 (1.75–2.60)	1.59 (1.49–1.62)	2.24 (2.06–2.44)	3.46 (3.10–3.81)	<0.001
Heart rate, bpm	70 (56–89)	56 (51–71)	70 (58–84)	80 (71–90)	<0.001
Stroke volume, mL	56 (45–75)	51 (40–58)	60 (48–73)	79 (46–86)	0.026
LVEF, %	56 (47–62)	58 (37–63)	55 (50–62)	56 (46–59)	0.84
<50%, *n* (%)	36 (27)	11 (33)	17 (23)	8 (31)	0.51
Dilated CMP	14 (11)	5 (15)	7 (10)	2 (8)	
Ischaemic CMP	15 (11)	5 (15)	7 (10)	3 (12)	
Left valvular heart disease	6 (5)	1 (3)	2 (2)	3 (12)	
Restrictive CMP	1 (1)	0	1 (1)	0	
TAPSE, mm	17 (±5)	16 (±5)	16 (±5)	18 (±6)	0.18
<17 mm, *n* (%)	67 (51)	19 (58)	38 (51)	10 (38)	0.41
RV diameter, mm	43 (39–48)	42 (40–44)	44 (37–49)	44 (40–48)	0.80
Vena cava diameter, mm	28 (±8)	26 (±7)	27 (±6)	32 (±10)	0.003
TR grade, *n* (%)					0.59
III	112 (85)	30 (91)	62 (85)	20 (77)	
IV	20 (15)	3 (9.1)	11 (15)	6 (23)	
TR EROA, mm^2	0.50 (0.40–0.70)	0.40 (0.36–0.60)	0.52 (0.40–0.76)	0.49 (0.43–0.70)	0.31
TR vena contracta, mm	9.00 (8.00–12.00)	8.60 (7.00–10.00)	9.00 (8.00–12.00)	10.00 (8.00–12.00)	0.17
Tricuspid regurgitant volume, mL	47 (±18)	45 (±19)	48 (±20)	48 (±15)	0.69
Coaptation gap, mm	6 (±3)	5 (±3)	6 (±3)	5 (±2)	0.88
Concomitant MR ≥II, *n* (%)	39 (30)	7 (23)	17 (27)	10 (42)	0.26
Haemodynamics					
CI, mL/min/m^2	2.3 (±1)	1.4 (±0.2)	2.1 (±0.3)	3.5 (±0.9)	<0.001
Stroke work, mmHg*mL	11 (6–17)	8 (4–12)	12 (8–16)	16 (11–21)	0.002
SBP, mmHg	130 (115–146)	126 (115–147)	132 (120–151)	118 (111–128)	0.031
MAP, mmHg	86 (80–101)	90 (84–106)	90 (82–105)	78 (69–82)	<0.001
Systolic PAP, mmHg	46 (36–59)	43 (35–55)	46 (35–59)	49 (42–62)	0.27
TAPSE/PAPs	0.35 (0.25–0.49)	0.36 (0.27–0.51)	0.33 (0.23–0.50)	0.41 (0.27–0.46)	0.83
<0.29, *n* (%)	41 (31)	11 (33)	24 (33)	6 (23)	0.62
Diastolic PAP, mmHg	20 (15–25)	19 (14–25)	19 (16–24)	24 (20–28)	0.08
Mean PAP, mmHg	30 (24–38)	29 (23–39)	30 (23–36)	32 (29–40)	0.23
PCWP, mmHg	20 (15–25)	22 (14–25)	19 (16–24)	20 (15–25)	0.87
RAP mean, mmHg	15 (11–21)	14 (11–17)	15 (10–20)	17 (12–24)	0.28
SVR, dyne*s/cm^5	1726 (1332–2478)	2528 (2105–2662)	1521 (1319–1892)	783 (559–810)	<0.001
PVR, dyne*s/cm^5	196 (153–288)	263 (172–374)	191 (144–272)	173 (130–226)	0.11

CI, cardiac index; CMP, cardiomyopathy; EROA, effective regurgitant orifice area; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MR, mitral regurgitation; PAP, pulmonary artery pressure; PAPs, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; SBP, systolic blood pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Based on invasive assessment, median CI was 2.03 (1.70–2.57) L/min/m^2 and correlated well with echocardiographic CI calculations (r = 0.85, $P < 0.001$). Bland–Altman plot analysis of both methods are presented in online supplementary *Figure S1*. An interobserver variability analysis of the echocardiographic measurements showed an intra-class correlation coefficient of 0.98 (95% confidence interval 0.96–0.99) and a mean squared error of 33, resulting in a mean measurement error of 7.5%.

K-means clustering according to CI derived from LVOT-based stroke volume calculations revealed three clusters: 33 patients were stratified to the low (median CI 1.5, from 1.0 to <1.7 L/min/m^2), 73 to the intermediate (median CI 2.1, range 1.7–2.6 L/min/m^2) and 26 patients to the high CO cluster (median CI 3.4, range 2.6–6.4 L/min/m^2). The higher CI in the high CO cluster was driven by both increased stroke volume as well as heart rate (*Table 2*).

Clinical characteristics of different cardiac output states

Baseline characteristics of the three clusters are presented in *Table 1*. Patients in the high CO state were younger and were

more often males as compared to lower CO states. There were no differences in NYHA class, body mass index and EuroSCORE II in patients across different CO states. The prevalence of chronic pulmonary disease was comparable between patients in different CO states. On laboratory analysis, patients in the high CO cluster exhibited more pronounced signs of chronic liver congestion (higher levels of alkaline phosphatase; $P = 0.01$) and reduced liver function with lower cholinesterase levels ($P = 0.01$). There was a significant difference between low and high CO state patients in GGT with higher levels in the high CO cluster ($P = 0.05$). Clinically evident ascites was most frequent in high CO state patients (46%, $P = 0.006$). There were no significant differences in eGFR between the different CO states. Also, despite marked differences in CI, NT-proBNP levels were comparably elevated without significant differences among CO clusters.

Echocardiographic findings of cardiac index-based tricuspid regurgitation phenotypes

Overall, there was no difference in left ventricular function and genesis of impaired left ventricular ejection fraction as displayed in more detail in *Table 2*. Right ventricular function and size were balanced across different CO states. In comparison to low CO state patients, high CO state patients were characterized by significantly larger inferior vena cava diameters ($P = 0.003$). Quantitative assessments of TR were similar among the different CO states. Performing clustering according to invasively derived CI yielded comparable results as outlined in online supplementary *Table S1*.

Haemodynamics and procedural outcomes according to cardiac output state

As compared to intermediate and low CO state patients, systemic vascular resistance was markedly reduced in patients with a high CO state phenotype of TR ($P < 0.001$; *Table 1*). In contrast, baseline haemodynamics displayed comparable pulmonary artery and pulmonary capillary wedge pressures between CI clusters of TR. Pre-procedural RAP showed no difference across CO states.

The number of devices implanted during TTVR, or their respective locations, did not differ between CO states. Overall, 130 patients (98%) received TTVR using the MitraClip device and 2 (2%) the PASCAL device. During TTVR, TR was reduced by a comparable extent among the CO states (*Figure 1A,B*). Interestingly, while the postprocedural haemodynamic response was comparable between patients in the low and intermediate CO states, it differed significantly in high CO state patients. Post-interventional RAP and right ventricular diameters were significantly reduced after TTVR in both low and intermediate CO state patients. However, high CO state patients did neither respond with reduced RAP nor with right ventricular diameter reduction following TTVR, despite a similar decline in EROA and TR volume (*Figure 1C,D*). This observation was reflected by a significantly lower extent of RAP as well as right ventricular diameter reduction per regurgitant volume reduction

for high CO state patients, when compared to the other CO states (*Figure 1E,F*).

Prognostic implications of cardiac index

After 1-year of follow up, 27 (20%) patients died. Cox regression showed a counter-intuitive harmful effect of higher CI on mortality [hazard ratio 1.6 (95% confidence interval 1.1–2.4]), $P = 0.01$) in the overall non-clustered cohort. In a multivariable Cox regression analysis, CI remained a strong predictor of mortality even after adjusting for several other covariates (*Table 3*, online supplementary *Table S2*).

Albeit procedural success was evenly distributed among patients in the different CO states, it conveyed different prognostic implications in each cluster. Cross validation of the cumulative risk demonstrated a U-shaped interaction of mortality and CI with the highest mortality rates for patients in the low and high CO clusters. Kaplan–Meier analysis yielded the highest rate of death in the high CO cluster followed by the low CO, whereas mortality was lowest for the intermediate CO cluster (*Figure 2A,B*). This result was reproducible when the analysis was repeated with CI clustering performed by invasively derived CI (online supplementary *Figure S2*). The beneficial effect of procedural success on mortality was reduced in patients with low and high CO state with overlapping confidence intervals for procedural success and failure, demonstrating the most favourable response to successful TTVR in intermediate CO state patients (*Figure 2C*). However, NYHA functional class improved to similar degrees alongside all CO states.

Similar results were made when observing hospitalizations for decompensated heart failure and a combined endpoint of heart failure hospitalizations and death as shown in online supplementary *Figure S3*. Further univariable predictors for all-cause mortality and a combination of all-cause mortality and heart failure hospitalization are displayed in online supplementary *Table S3*.

Discussion

By using a supervised machine learning-based approach, the present study is the first to provide a CI-based phenotyping of patients with symptomatic right heart failure complicated by severe functional TR. This novel classification suggests the presence of three CO state clusters of patients being associated not only with the clinical hallmark of this type of heart failure (i.e. marked chronic venous congestion), but also with the haemodynamic impact and clinical outcome of a therapeutic intervention.

The main findings of the present study can be summarized as follows:

(i) Clustering reveals low, intermediate and high CO state phenotypes in patients with symptomatic right heart failure and severe TR with the high CO state phenotype being characterized by markedly reduced systemic vascular resistance.

(ii) The high CO state phenotype is associated with a biochemical marker pattern suggestive of congestive hepatopathy, impaired liver function and clinical evidence of portal hypertension (i.e. a higher grade of ascites).
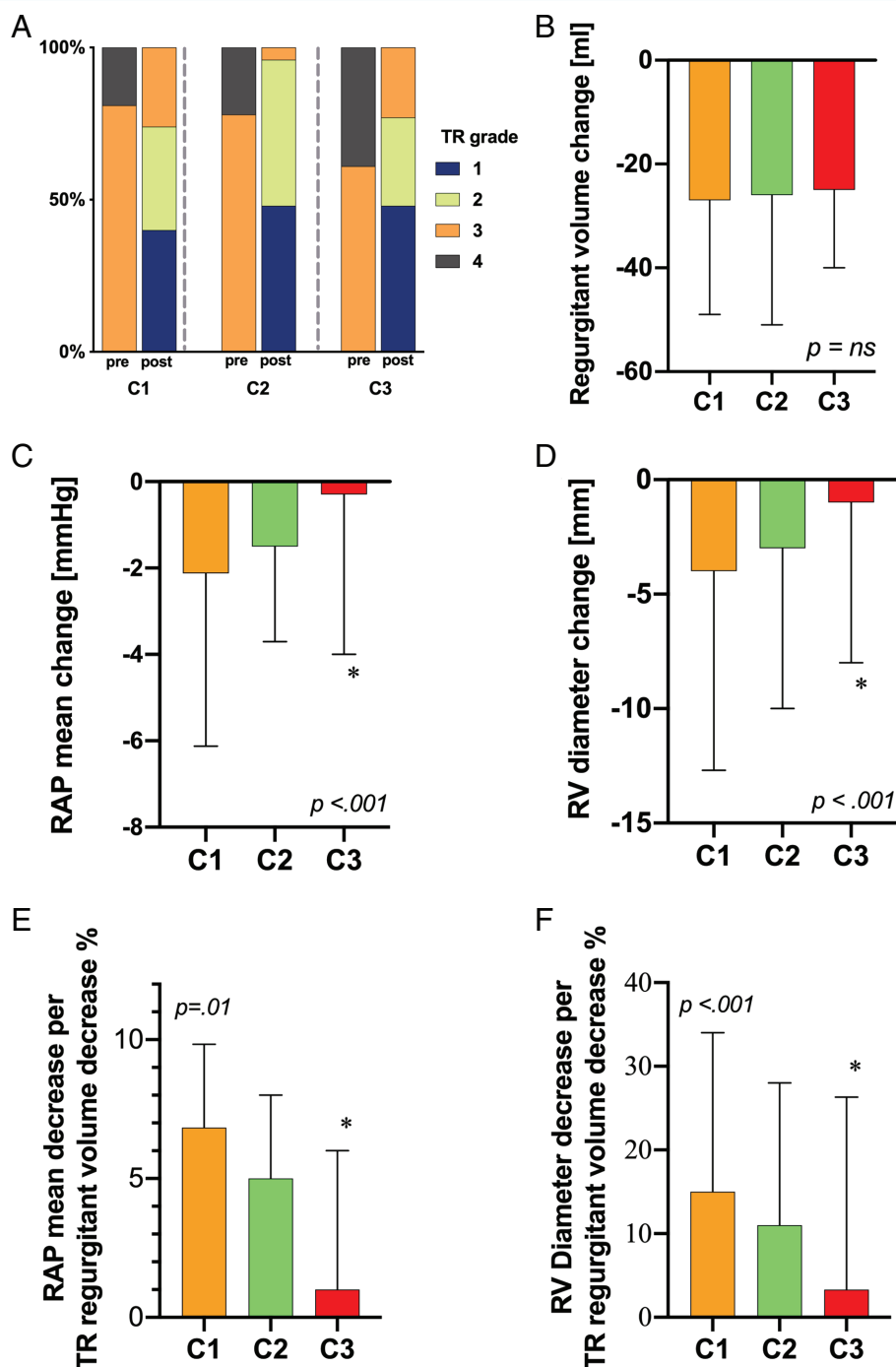
Figure 1 Comparison of pre- and post-interventional measurements. (*A*) Pre- and post-interventional tricuspid regurgitation (TR) grade distribution among different cardiac index (CI) clusters. (*B*) TR volume change between different CI clusters. (*C*) Right atrial pressure (RAP) changes in CI clusters. (*D*) Right ventricular (RV) diameter changes according to different CI clusters. (*E*) RAP decrease per TR volume decrease in percent. (*F*) RV diameter decrease per TR volume decrease in percent. C1, cluster 1 (low cardiac output state, CI <1.7 L/min/m²); C2, cluster 2 (intermediate cardiac output state, CI 1.7–2.6 L/min/m²); C3, cluster 3 (high cardiac output state, CI >2.6 L/min/m²).

Table 3 Multivariable analysis of predictors for all-cause mortality

	HR	95% CI	P-value
Model 1: Clinical findings			
Cardiac index cluster			
Low cardiac output state	2.28	0.79–6.59	0.13
Intermediate cardiac output state	1.0	–	–
High cardiac output state	4.72	1.75–12.7	0.002
NYHA class	1.42	0.62–3.25	0.40
Peripheral oedema	0.83	0.31–2.19	0.71
BMI	0.92	0.84–1.01	0.094
Ascites	1.75	0.67–4.56	0.25
Model 2: Laboratory findings			
Cardiac index cluster			
Low cardiac output state	2.94	0.68–12.7	0.15
Intermediate cardiac output state	1.0	–	–
High cardiac output state	7.31	1.77–30.1	0.006
NT-proBNP	1.94	0.97–3.91	0.062
Alkaline phosphatase	1.00	1.00–1.01	0.81
Cholinesterase	0.66	0.44–1.01	0.055
GOT	1.00	0.94–1.06	0.92
GPT	1.01	0.95–1.07	0.76
GGT	1.00	1.00–1.00	0.86
Model 3: Echo parameters			
Cardiac index cluster			
Low cardiac output state	1.92	0.58–6.37	0.29
Intermediate cardiac output state	1.0	–	–
High cardiac output state	6.61	2.23–19.6	<0.001
LVEF	1.01	0.97–1.04	0.75
TAPSE	0.96	0.87–1.06	0.39
MR grade	1.46	0.79–2.70	0.22
Systolic PAP	1.02	1.00–1.05	0.10

BMI, body mass index; CI, confidence interval; GGT, gamma-glutamyl transferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamate-pyruvate transaminase; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

(iii) The haemodynamic response after successful TTVR differs between CO states, with attenuated preload reduction despite effective TR treatment being evident in patients with a high CO state.

(iv) Outcome after TTVR is associated with pre-procedural CI in a bimodal fashion with increased mortality for both patients in a low and high CO state, and highest overall mortality for patients with a high CO state phenotype.

Assessment and alterations of cardiac index in functional tricuspid regurgitation

Cardiac index is a well-established parameter to assess the cardiocirculatory state as well as to predict outcome in heart failure patients, with lower CI being associated with increased mortality in a linear fashion.[14] A recently published retrospective analysis investigating the prognostic impact of TR severity on heart failure hospitalization and mortality in 33 305 patients suggested that CO, derived from LVOT stroke volume calculations, declines with increasing TR severity.[15] Although no data on body surface area are provided in this publication, mean CO was 4.1 L/min in patients with severe TR. Assuming a body surface area of 1.9 m², calculation
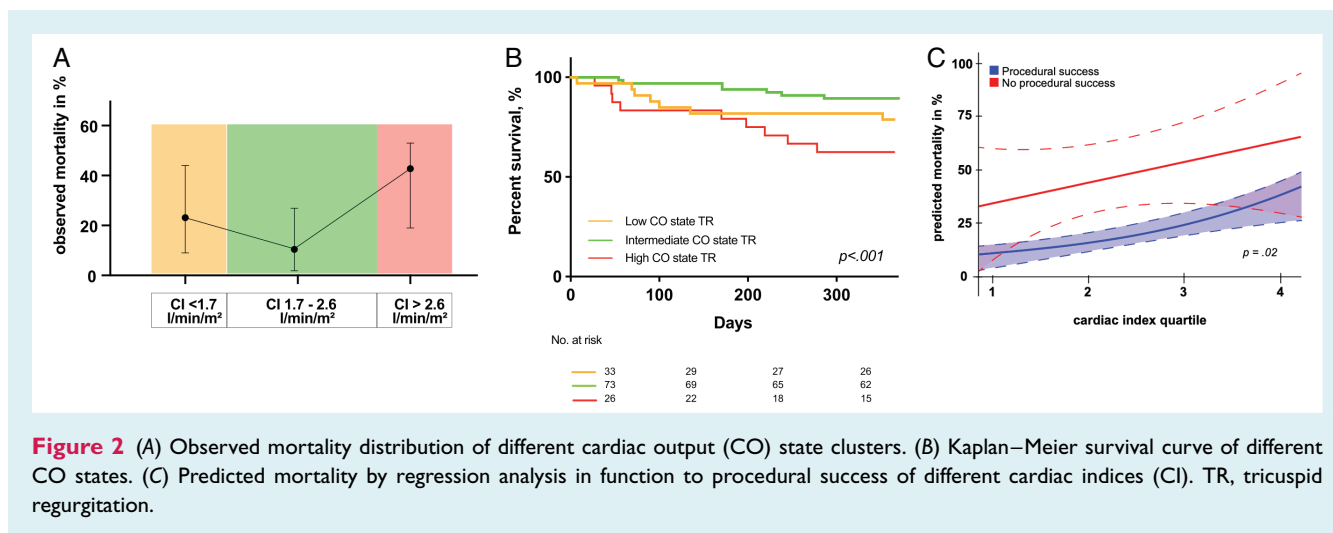
of CI would yield a mean value of 2.1 L/min/m², which is very similar to the CI observed in the present cohort of patients with severe TR. Notwithstanding such decline in CI with increasing TR severity assessed with the traditional three-tiered TR grading scheme, the distribution of CI among patients with symptomatic right heart failure and severe or massive/torrential long-standing TR has never been addressed specifically.

The present data suggest that a reduction of CI is not ubiquitous in these patients. Rather, CI-based clustering analyses based on supervised machine learning classifies patients with symptomatic right heart failure and severe TR into three groups, which we termed low, intermediate and high CO state phenotype. Notably, 20% of patients displayed a high CO state phenotype, being characterized by a CI of ≥2.6 L/min/m² in the presence of markedly elevated right heart filling pressures and reduced systemic vascular resistance.

The calculation of CI in patients with symptomatic heart failure and moderate or severe TR has been subject of intense discussion throughout the last decades. We primarily focused on an echocardiographic assessment as it can be easily obtained in clinical practice. Invasive CI values correlated very well with echocardiographic CI assessment (r = 0.85) and sensitivity analysis confirmed prognostically relevant high CO states even when CI was measured invasively. Altogether, this supports the validity of non-invasive and invasive CI measurements in the present study and the clustering of patients into different CO states.

High-output heart failure and prognosis

Counterintuitively, patients with severe symptomatic functional TR and an apparently preserved CI display worse prognosis in the present analysis when compared to patients in the low or intermediate CO state cluster. Such observations of an inverse association between elevated CI and outcome in patients with heart failure are not entirely new. In addition to recent data on a U-shaped association between left ventricular ejection fraction and mortality derived from electronic health records,[16] a subset of patients with typical clinical signs of heart failure presents with a marked elevation of CI, a condition known as high-output heart failure. Recently, a high CO has been associated with higher long-term mortality in the natural course of patients with isolated secondary TR and left ventricular ejection fraction ≥ 40%.[17] Excessive systemic vasodilatation is considered both as a central pathophysiological feature of this cause of cardiac failure and a major determinant of prognosis.[18] Yet, CI levels of patients in the present analysis are substantially lower when compared to patients with high-output heart failure, which is reasonable considering the fact that cardiac injury in the majority of patients with high-output heart failure is rather a consequence of an underlying extracardiac disease, such as obesity, arteriovenous shunts and liver disease.[18] In contrast, patients with long-standing right heart failure accompanied by functional TR are in a quite advanced state of cardiac impairment and, hence, the haemodynamic profile observed in the high CO state cluster may be viewed as a relative high-output state induced by peripheral vasodilatation in the presence of an actually depressed cardiac function.

Figure 2 (*A*) Observed mortality distribution of different cardiac output (CO) state clusters. (*B*) Kaplan−Meier survival curve of different CO states. (*C*) Predicted mortality by regression analysis in function to procedural success of different cardiac indices (CI). TR, tricuspid regurgitation.

Potential mechanisms underlying a high cardiac output phenotype of right heart failure complicated by tricuspid regurgitation

The present study was not designed to provide mechanistic insights into the pathogenesis of different CO state phenotypes among patients with right heart failure complicated by TR. As such, data on the interaction between chronic venous congestion, its extra-cardiac implications, CO and peripheral vascular tone obtained in the present study do not provide a causal or temporal relationship.

Nevertheless, when interpreted in the context of the pre-existing literature on pathophysiological implications of chronic right heart failure, several potential explanations may account for the concept of different CO state phenotypes proposed in the present study. First, patients in a high CO state are characterized by more pronounced markers of congestive hepatopathy, such as a cholestatic laboratory profile,[19–21] and this cardio-hepatic interaction may contribute to alterations in the CO state. According to the findings obtained on histopathological analysis, chronic venous congestion in right heart failure leads to sinusoidal dilatation, centrilobular and sinusoidal fibrosis, and hepatocyte atrophy. Changes of this tightly regulated cellular and molecular network have been suggested to affect systemic vascular resistance, e.g. in the hyperdynamic syndrome observed in patients with liver cirrhosis.[22–24] Therefore, congestive hepatopathy, as observed in patients with advanced right heart failure, may result in a disequilibrium of vasoactive substances in favour of vasodilatation leading to the profound decrease in systemic vascular resistance observed in the present study. Interestingly, this may also affect the splanchnic vascular bed,[25] resulting in a shift between stressed and unstressed splanchnic blood volume.[26]

Second, patients with chronic right heart failure display an impaired intestinal barrier function (also known as the 'leaky gut') due to chronic venous congestion.[27] As a result, intestinal congestion has been linked to a chronic low-grade systemic inflammatory state mediated, at least in part, by translocation of gut microbiota components and the presence of bacterial products in the systemic circulation.[27] Systemic inflammation induces well-characterized vascular changes via circulating inflammatory mediators, including vasodilatation, increased permeability and increased blood flow. These changes may serve as another potential explanation for the hypercirculatory subphenotype of patients with chronic right heart failure and TR described in the present study.

Third, splanchnic vasodilatation results in relative hypovolaemia and reduced glomerular perfusion.[28] Subsequently, the compensatory activation of the renin−angiotensin−aldosterone system with renal sodium and water retention increases fluid retention, driving the splanchnic capacitance to the upper limits. Lastly, due to the following sympathetic activation, a considerable shift of flow from the splanchnic reservoir to the central circulation might occur.[25,29] This ultimately leads to a vicious cycle of increasing preload, and markedly reduced afterload through systemic resistance decrease and the rise in contractility with fluid shift by sympathetic activation together result in increased heart rate as well as stroke volume.[18] The sum of these mechanisms that comprise increased preload, reduced afterload and a rise in sympathetically mediated myocardial contractility possibly explain the observed increase in CO (*Graphical Abstract*).

Response to transcatheter tricuspid valve repair in hypercirculation

Notably, the present data suggest that the haemodynamic benefit derived from TTVR varies according to the respective CO state. Patients with a high CO state experience less preload reduction (as estimated by RAP and right ventricular dimensions) despite a similar degree of TR reduction in comparison to patients with an intermediate or low CO state. Hypervolaemia might serve as a relevant driver of congestion in hypercirculatory patients as systemic and splanchnic buffering capacitance is diminished as discussed above, impairing the reduction in preload observed in non-hypercirculatory TR following TTVR. Reversibility of the consequences of chronic venous congestion might be limited

after the development of irremediable pathophysiological changes, either on a cardiac or extracardiac level. Unfortunately, such a point of no return remains yet to be defined. Future studies are needed to address the question whether adverse consequences of long-standing right heart failure in this setting result in fixed alterations of peripheral vascular tone, circulating blood volume and venous preload, making therapeutic interventions targeting TR futile.

Study limitations

Despite comparable patient numbers to recently published studies in the field of TTVR, the overall sample size remains limited. In addition, inferior vena cava diameter and RAP are estimates of volume status. However, to date there is no readily available method for the measurement of volume status or splanchnic volume shift in the clinical setting, making assumptions on the circulating blood volume in the present study population difficult. Invasive CI measurements have been discussed to be erroneous in presence of severe TR which is why we only used them for cohort description and sensitivity analysis.[30] TTVR treatment effects were evaluated with comparison to procedural success and failure and not between TTVR and optimal medical therapy, which might have diluted possibly observable treatment effects.

Overall, findings should be considered as hypothesis generating at present. In addition, future studies are needed to confirm the diagnostic and prognostic relevance of the circulatory state.

Conclusion

This study proposes a novel CI-based classification of patients with symptomatic chronic right heart failure complicated by severe TR including three distinct CO phenotypes (low, intermediate and high CO state). Patients in the high CO state are characterized by advanced congestive hepatopathy, worse liver function and a marked decrease in peripheral vascular tone. Such a classification appears to be of clinical relevance, as patients in the high CO state gain less benefit from TTVR, i.e. RAP and right ventricular dimensions remain similar despite sufficient TR reduction during TTVR. Finally, patients with a high CO state phenotype have a poorer outcome as compared to patients in the intermediate and low CO state cluster. These data advance our pathophysiological understanding of patients with severe TR and advanced right heart failure and may improve the therapeutic management of these patients in the future. Additional studies are warranted to confirm these results in a larger set of patients and to elucidate potential mechanisms sustaining the high CO state.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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