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ORIGINAL ARTICLE

Functional improvement following direct interventional leaflet repair of severe tricuspid regurgitation

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Abstract

Aims Several new percutaneous tricuspid repair systems have recently been introduced as new treatment options for severe tricuspid regurgitation (TR). Clinical improvement following percutaneous tricuspid valve leaflet repair has been demonstrated by recent studies. A possible impact on exercise capacity has not yet been reported.

Methods and results Eleven patients with at least severe TR and successful tricuspid leaflet repair using the PASCAL Ace implant at our cardiology department were included in this analysis. All patients suffered from symptomatic right-sided heart failure with compromised exercise capacity. Cardiopulmonary exercise testing (CPET), clinical, laboratory, and echocardiographic parameters were assessed at baseline and 3 months follow-up. The primary endpoint was the change in maximal oxygen consumption [VO_2 max (mL/(min*kg))] at 3 months follow-up. Secondary endpoints included improvement in TR, cardiac biomarkers, and other clinical outcomes. TR severity at 3 months follow-up post-PASCAL Ace implantation was significantly lower than at baseline (P = 0.004). Cardiac biomarkers including high-sensitivity troponin T and N-terminal pro-brain natriuretic peptide as well as right ventricular diameter improved slightly without reaching statistical significance (P = 0.89, P = 0.32, and P = 0.06, respectively). PASCAL Ace implantation resulted in a significant improvement in cardiopulmonary exercise capacity at 3 months follow-up compared with baseline. Mean VO_2 max improved from 9.5 ± 2.8 to 11.4 ± 3.4 mL/(min*kg) (P = 0.006), VO_2 max per cent predicted from 42 ± 12% to 50 ± 15% (P = 0.004), peak oxygen uptake from 703 ± 175 to 826 ± 198 mL/min (P = 0.004), and O_2 pulse per cent predicted from 67 ± 21% to 81 ± 25% (P = 0.011). Other CPET-related outcomes did not show any significant change over time.

Conclusions In this single-centre retrospective analysis, direct tricuspid valve leaflet repair using the transcatheter PASCAL Ace implant system was associated with a reduced TR severity and improved cardiopulmonary exercise capacity.

Keywords Tricuspid valve repair; Cardiopulmonary exercise testing; Percutaneous valve repair; Heart failure

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Introduction

Tricuspid regurgitation (TR) is common, with a prevalence of approximately 1.6 million in the USA. Large epidemiologic studies demonstrated a prevalence of trace level TR or higher of more than 60% in the western population.[1–3] It therefore represents one-fourth of all valvular heart diseases.[1] While severe to torrential TR is less frequent, it is still a common finding, especially in heart failure patients.[4] Severe or greater TR is linked to a poor prognosis with an estimated 5 year survival rate of <30% and a hazard ratio of 1.17 compared with individuals without relevant TR.[1] Retrospective analyses demonstrated similar findings, especially in heart failure patients.[5] Treatment options have so far been mostly limited

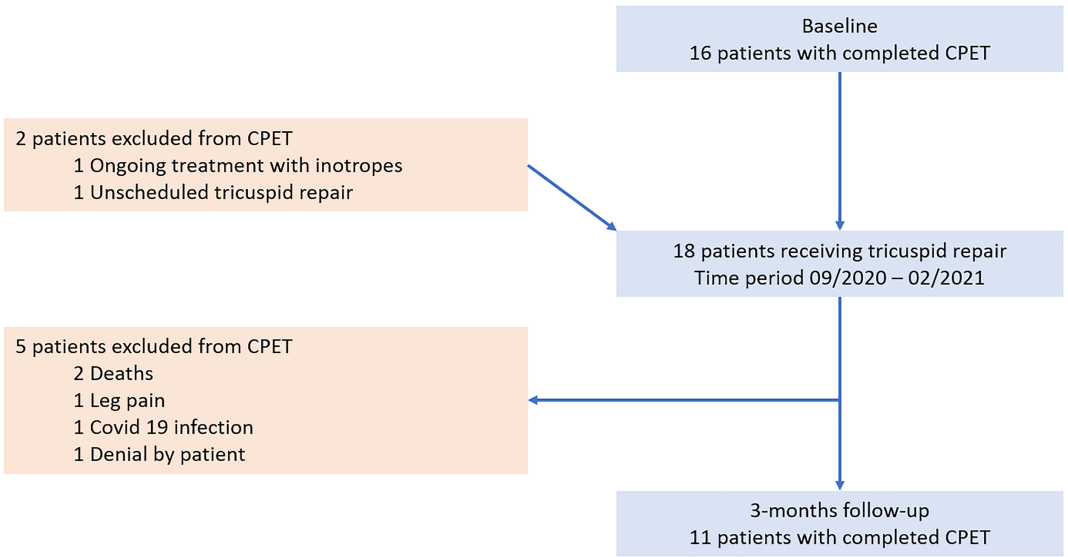
to surgical tricuspid repair in the setting of left-sided heart surgery. This approach has been validated by a meta-analysis of retrospective studies and was also included in recent guidelines.[6,7] In contrast, evidence for the treatment of isolated TR is still sparse and surgery has so far only been considered in severely symptomatic patients with severe or greater primary TR or with secondary TR in the presence of progressive right ventricular (RV) failure.[8]

In the last years, several percutaneous tricuspid repair systems have been introduced. In 2020, the edge-to-edge tricuspid valve repair systems TriClip (Abbott Vascular, North Chicago, IL, USA) and PASCAL (Edwards Lifesciences, Irvine, CA, USA) were introduced and initial studies also pointed to significant clinical und functional improvements at early follow-up.[9,10] Recently, PASCAL Ace (Edwards Lifesciences, Irvine, CA, USA) with narrower profile and slightly longer clasps compared with the original PASCAL implant was introduced and initial experiences with this device for treatment of severe, symptomatic TR were promising.[11] However, the impact of transcatheter tricuspid repair on functional capacity remains to be elucidated. Cardiopulmonary exercise testing (CPET) is an established tool to assess functional capacity and prognosis in heart failure patients.[12,13] We here present our single-centre experience and 3 months follow-up data using PASCAL Ace for direct tricuspid leaflet repair with focus on functional outcome assessed by CPET.

Methods

The study conforms with the principles outlined in the Declaration of Helsinki. The present investigation was conducted as single-centre study and was performed in a retrospective approach. The study was approved by the local ethics committee. Between September 2020 and February 2021, 18 patients underwent direct interventional leaflet tricuspid valve repair for severe or greater TR with the PASCAL Ace device at our institution. Complete CPET was performed in 11 out of 18 patients at baseline and 3 months follow-up. Seven patients were excluded from the analysis because CPET was not performed either at baseline or at follow-up. Two patients died before follow-up, one due to cardiogenic shock and another patient following sepsis. Two patients could not complete CPET at follow-up, one suffering from Covid-19 and the second due to severe leg pain. Another patient refused CPET due to severe allergic reaction to electrode patches. We did not perform exercise testing in one case because of ongoing treatment with inotropes and a further patient received unscheduled tricuspid edge-to-edge repair within the same procedure of transcatheter mitral valve repair. Patient flow is illustrated in *Figure 1*. All patients included were remarkedly limited in their daily life due to symptoms of right-sided heart failure. To assess eligibility, 3D transesophageal echocardiography was performed. Patients were offered PASCAL Ace treatment if the interventionalist considered interventional direct leaflet repair technically feasible and safe. A systolic pulmonary artery (PA) pressure $>$ 60 mmHg was defined as an exclusion criterium to avoid early RV failure. Patients included showed a high operative risk and were therefore not considered for cardiac surgery by the heart team. Patients gave written and informed consent for the procedure. All patients were assessed at baseline as well as 3 months after the intervention at our outpatient department. Primary endpoint was the change in peak oxygen uptake in CPET at 3 months follow-up vs.

Figure 1 Patient flow. CPET, cardiopulmonary exercise testing.



baseline before device implantation. Secondary endpoints included changes in New York Heart Association (NYHA) functional class, echocardiographic outcomes, as well as changes in cardiac biomarkers and kidney function.

Procedures

Procedures were performed under general anaesthesia to allow optimal echocardiographic guidance using transesophageal echocardiography. The PASCAL Ace implant system consists of a 22 F guide sheath with a steerable guide catheter and an implantation catheter to access the tricuspid valve via a transfemoral venous approach. TR reduction was achieved by approximation of the anterior and septal leaflet and/or posterior and septal leaflet. Up to three PASCAL Ace devices were used if needed. The procedure was performed under transesophageal echocardiographic and fluoroscopic guidance. Access site closure was achieved by applying one ProGlide SH closure device (Abbott Vascular, North Chicago, IL, USA) using the preclosure technique.

Echocardiographic workup

Prior to implantation, all patients were screened using transesophageal and transthoracic echocardiography. TR severity was evaluated using the size of the regurgitation area, vena contracta width, and inferior vena cava variability as well as hepatic vein flow patterns. In addition, TR severity was divided into five grades according to the recently proposed staging system by Hahn and Zamorano using the additional grades 'massive' and 'torrential'.[14] Technical feasibility prior to PASCAL Ace implantation was additionally assessed using biplane transgastric short axis, deep midesophageal, as well as transthoracic images, as previously described.[15] Biplane transgastric and deep midesophageal views were used for intraprocedural guidance. Follow-up transthoracic echocardiography was conducted 3 months after the procedure according to ASE/ESC guidelines.[16]

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing has been reported to be a reliable tool to assess cardiopulmonary functioning and predict mortality in heart failure patients.[12,17] A relationship to RV functioning has also been reported.[13] Symptom-limited CPET was performed using Oxycon Pro® (Jaeger Healthcare GmbH). The protocol started with a resting period of 2 min followed by a reference cycling period with leg movement without workload. The test period started at a workload of 15 W; power was increased by 15 W every 2 min. Electrocardiogram and blood pressure were documented before, continuously during, and after exercise. Anaerobic threshold was identified using the respiratory exchange ratio (RER). Minute ventilation-to-carbon dioxide output (VE/VCO_2) slope was calculated from start to anaerobic threshold via least squares linear regression. Peak oxygen pulse (O_2 pulse) was calculated as peak VO_2 divided by peak heart rate and expressed as per cent of predicted value. Peak oxygen uptake (VO_2 peak) was expressed as mL/min and mL/(min*kg) (VO_2 max) as well as per cent of predicted value. Predicted values were estimated by a gender-adjusted, age-adjusted, and height-adjusted and protocol-specific formula. Maximum voluntary ventilation (MVV) was estimated as forced expiratory volume (FEV1) * 40.

Clinical workup and biomarkers

Data assessment included medical history, diuretics use, NYHA functioning class at baseline and 3 months follow-up, and the following biomarkers: N-terminal pro-brain natriuretic peptide (NT-proBNP) (reference $<$ 125 ng/L for age $<$ 75 years, $<$450 ng/L for age $>$ 75 years), high-sensitivity troponin T (hsTNT) (reference $<$ 14 pg/mL; 3–50 pg/mL observational zone; $>$50 pg/mL elevated), bilirubin (reference $<$ 1.0 mg/dL), and serum creatinine (reference 0.6–1.3 mg/dL). Glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease formula.

Statistics

Continuous data are expressed as mean and standard deviation, and categorical variables as absolute numbers and percentages. Comparison between baseline and follow-up data was performed using Wilcoxon signed rank test or paired Student's *t*-test as needed. Graphics were designed using RStudio Team,[18] the package ggpubR,[19] as well as the package ggplot2.[20]

Results

Patient population

Eleven patients with severe or greater secondary TR underwent interventional direct tricuspid valve leaflet repair with the PASCAL Ace implant and completed CPET at baseline and follow-up. Mean age was 71 ± 9 years. Baseline characteristics are listed in *Table 1*. All patients presented with a very limited cardiopulmonary exercise capacity at baseline with a mean VO_2 max of 9.5 ± 2.8 mL/(min*kg), VO_2 peak 703 ± 175 mL/min, 42 ± 12% predicted, O_2 pulse of 67 ± 21% of predicted maximum, and elevated VE/VCO_2 slope (39 ± 9).[12,21] All CPET results are given in detail in *Table 2*. All 11 patients presented with NYHA functional class III. Cardiac

Table 1 Pre-interventional and post-interventional characteristics of the study population

Parameter	Pre-intervention (n = 11)	3 months follow-up (n = 11)	P-value*
Clinical data			
Female, n (%)	3 (27%)		
Age, years	71 ± 9		
BMI	25 ± 3		
BP systolic, mmHg	121 ± 21		
BP diastolic, mmHg	71 ± 6		
Heart rate, min^{-1}	76 ± 18		
EuroSCORE II, %	5.5 ± 3.7		
Beta-blocker use	7 (63%)	9 (82%)	0.42
ACE/AT-1 inhibitor use	4 (36%)	6 (55%)	0.42
Mineralocorticoid receptor antagonist use	5 (45%)	7 (63%)	0.42
Loop diuretics use	10 (91%)	10 (91%)	1
NYHA, functional class			0.006
I, n (%)			
II, n (%)		7 (63%)	
III, n (%)	10 (91%)	4 (36%)	
IV, n (%)	1 (9%)		
Comorbidities			
CAD, n (%)	8 (73%)		
Atrial fibrillation, n (%)	7 (63%)		
ICD/PM, n (%)	5 (45%)		
COPD, n (%)	4 (36%)		
Renal failure, n (%)	5 (45%)		
Cardiac biomarkers			
hsTNT, pg/mL	48 ± 30	44 ± 30	0.89
NT-proBNP, ng/L	5163 ± 4278	3856 ± 2798	0.32
Echocardiography			
RV diameter, mm	49 ± 6	45 ± 7	0.06
TAPSE, mm	1.6 ± 0.4	1.5 ± 0.4	0.44
EF, %	43 ± 15	44 ± 14	0.40
Systolic PA pressure	49 ± 11	46 ± 13	0.94
Tricuspid regurgitation, grade			**0.004**
I, n (%)		6 (55%)	
II, n (%)		3 (27%)	
III, n (%)	3 (27%)	1 (9%)	
IV, n (%)	5 (45%)	1 (9%)	
V, n (%)	3 (27%)		

ACE, angiotensin-converting enzyme; AT-1, angiotensin-1; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; hsTNT, high-sensitivity troponin T; ICD, implantable cardioverter defibrillator; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PM, pacemaker; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.
*P-values are the result of a paired Student's t-test or Wilcoxon signed rank test according to standard distribution between baseline and 3 months follow-up.

Table 2 Outcomes of cardiopulmonary exercise testing at baseline and 3 months follow-up

Parameter	Pre-intervention (n = 11)	3 months follow-up (n = 11)	P-value*
VO_2 max (mL/(min*kg))	9.5 ± 2.8	11.4 ± 3.4	0.006
VO_2 per cent predicted	42 ± 12	50 ± 15	0.004
VO_2 peak (mL/min)	703 ± 175	826 ± 198	0.004
Peak O_2 pulse per cent predicted	67 ± 21	81 ± 25	0.011
VE/VCO_2 slope	39 ± 9	38 ± 7	0.62
AT (mL VO_2/min)	639 ± 166	749 ± 193	0.17
AT (mL VO_2/min/kg)	8.7 ± 2.7	10.2 ± 3.3	0.32
Peak power (W)	48 ± 15	50 ± 17	0.56
Maximum heart rate (bpm)	97 ± 17	95 ± 19	0.74
Breathing reserve (%)	39 ± 19	32 ± 22	0.45
Peak respiratory rate (1/min)	29 ± 7	29 ± 7	0.90
MVV	73 ± 26	82 ± 33	0.53
FEV1 (L)	1.8 ± 0.6	2.1 ± 0.8	0.53
Systolic blood pressure at rest (mmHg)	127 ± 22	129 ± 20	1.00
Peak systolic blood pressure (mmHg)	130 ± 29	132 ± 29	0.98

AT, anaerobic threshold; FEV1, forced expiratory volume; MVV, maximum voluntary ventilation; VE/VCO_2, minute ventilation-to-carbon dioxide output; VO_2 max, maximal oxygen consumption; VO_2 peak, peak oxygen consumption.
*P-values are the result of a paired Student's t-test or Wilcoxon signed rank test according to standard distribution between baseline and 3 months follow-up.

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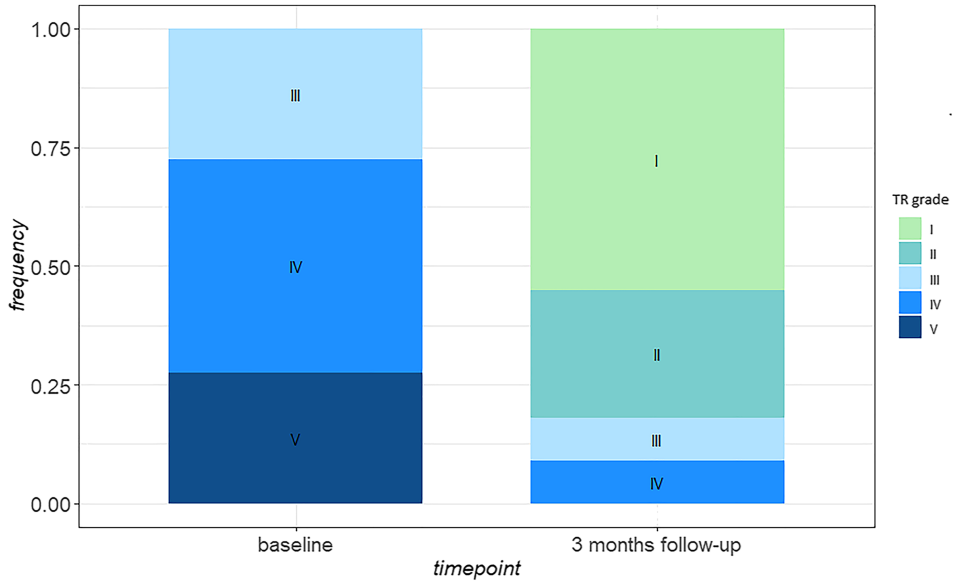
Figure 2 Tricuspid regurgitation grade at baseline and 3 months follow-up. Tricuspid regurgitation is displayed according to the newly proposed five-level grading system. TR, tricuspid regurgitation.



biomarkers were elevated (NT-proBNP 5163 ± 4278 ng/L, hsTNT 48 ± 30 pg/mL), and mean RV diameter was dilated (49 ± 6 mm). Patients included were all treated according to current heart failure guidelines. One patient underwent heart transplantation before interventional tricuspid leaflet repair suffering from recurrent humoral and cellular rejection with consecutive right-sided heart failure and severe TR. Two patients were suffering from cardiac wild-type transthyretin amyloidosis. Five patients included presented with ischaemic cardiomyopathy, one with dilated cardiomyopathy, one with hypertrophic cardiomyopathy, and one with isolated RV cardiomyopathy.

Technical outcomes, biomarkers, and safety

In four procedures, one device was implanted in anteroseptal position only. Five patients received one device in anteroseptal and one in posteroseptal position. In one case, two implants were placed in the anteroseptal position, and in one case, two in the anteroseptal and one in the posteroseptal position. At baseline, TR was torrential in three patients, massive in five patients, and severe in three patients. At follow-up, six patients presented with a TR of mild or trace level, three patients with moderate TR, one patient with severe TR, and one patient with massive TR. Improvement in TR at follow-up level reached statistical significance when compared with baseline level (P = 0.004). Changes in TR are illustrated in *Figure 2*.

Right ventricular diameter, tricuspid annular plane systolic excursion, ejection fraction, systolic pulmonary arterial pressure, as well as cardiac biomarkers including hsTNT and NT-proBNP showed no significant change at follow-up. Changes over time are listed in *Tables 1* and *2*.

Table 3 Cardiovascular safety outcome at 3 months follow-up

Event	Frequency
Mortality	2 (11%)
Myocardial infarction	0
Stroke	0
Major bleeding	0
Single leaflet detachment	1 (6%)

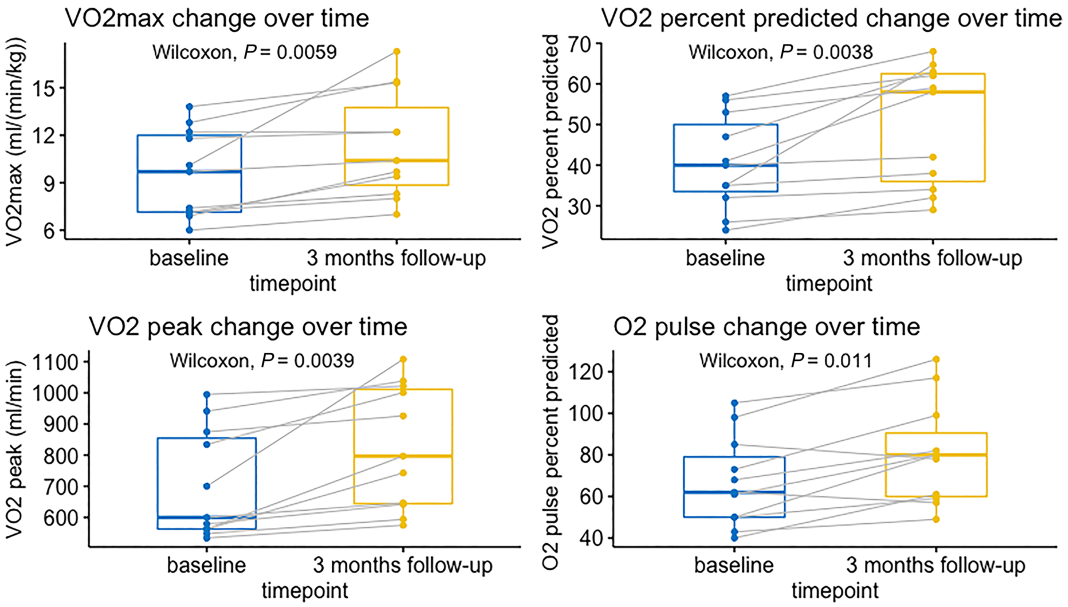
Values are given as absolute numbers and per cent.

At follow-up, one patient who was initially treated with two devices (one anteroseptal and one posteroseptal) presented with partial leaflet detachment of the posteroseptal device. In this case, the septal part of the PASCAL Ace device was detached resulting in massive TR. Safety results of all 18 patients undergoing edge-to-edge tricuspid repair are summarized in *Table 3*.

Functional capacity

Primary outcome was change in VO_2 max at 3 months follow-up compared with baseline. One patient did not reach a peak RER $\geq$ 1.0 during the 3 months follow-up test (RER 0.95). All other patients in all other CPET examinations reached symptom limit with RER $\geq$ 1.0. Following PASCAL Ace implantation, all 11 patients showed improved VO_2 max at follow-up resulting in significant overall improvement

Figure 3 Changes in cardiopulmonary exercise testing. Displayed are the results of cardiopulmonary exercise testing for peak oxygen uptake-related outcomes at baseline and 3 months follow-up. Predicted values were estimated by a gender-adjusted, age-adjusted, and height-adjusted and protocol-specific formula. Peak oxygen pulse was calculated as peak oxygen consumption divided by peak heart rate and expressed as per cent of predicted value. *P*-values are the result of a Wilcoxon signed rank test between baseline and 3 months follow-up. O_2 pulse, peak oxygen pulse; VO_2 max, maximal oxygen consumption; VO_2 peak, peak oxygen consumption.



(9.5 ± 2.8 mL/(min*kg) vs. 11.4 ± 3.4 mL/(min*kg), $P = 0.006$). Mean peak VO_2 improved from 703 ± 175 to 826 ± 198 mL/min ($P = 0.004$), VO_2 max per cent predicted from 42 ± 12% to 50 ± 15% ($P = 0.004$), and O_2 pulse per cent predicted from 67 ± 21% to 81 ± 25% ($P = 0.011$) (*Figure 3*). In accordance to these findings, 8 out of 11 patients presented with improved NYHA functional class at follow-up ($P = 0.006$). All other CPET-related outcomes did not show any significant improvement over time.

Discussion

In this investigation of 11 cases, we report the impact of interventional direct tricuspid repair for severe or greater TR using the PASCAL Ace implant on functional capacity as assessed by CPET. Recently, the TriClip device as well as PASCAL and PASCAL Ace have been introduced as novel transcatheter treatment options for severe or greater TR and several studies demonstrated the feasibility and safety of the different procedures.[9,11,22] CPET was established as a reliable tool for risk stratification in heart failure patients and holds important prognostic implications for this patient group.[12,23] Especially peak oxygen uptake and VE/CO_2 slope have emerged as important predictors for mortality, rehospitalization, and death.[23] To the best of our knowledge, this is the first report investigating the relationship between direct interventional tricuspid repair with PASCAL Ace system and cardiopulmonary exercise capacity.

For many years, interventional treatment options in valvular heart disease mainly focused on aortic and mitral valve diseases while treatment of TR was limited to surgical repair associated with a high perioperative risk.[24] Moderate to severe TR is a very common finding in heart failure patients with a prevalence of approximately 30%.[4] Five-year survival in this patient group has been estimated to be 45–34%, and therefore, further treatment options could play an important role in the future. Today, CPET parameters are used in a broad patient population for risk stratification especially in heart failure, selection of heart transplantation, and assist device candidates.

Out of 18 initially treated patients, 11 patients with severe TR could be included in this analysis. One patient experienced partial leaflet detachment within the 3 months follow-up period resulting in massive TR. In all other cases, a stable reduction in TR was achieved. Patients presented with severely compromised cardiopulmonary functioning. Following transcatheter direct tricuspid repair, we observed a significant improvement in peak VO_2-related outcomes including O_2 pulse. To our knowledge, an increase in cardiopulmonary exercise capacity following interventional tricuspid repair has not yet been reported. The prognostic implication of the improvement in VO_2 max in heart failure patients has been discussed before and cut-off values between 1 and 4 mL/(min*kg) have been suggested as relevant for clinical prognostic

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outcomes.[25,26] Therefore, the improvement of 1.9 mL/(min*kg) in this small patient group cannot clearly be rated as a clinically relevant improvement. However, the very limited exercise capacity at baseline, highly elevated cardiac biomarkers, and several comorbidities demonstrate that the investigated cohort clearly represents a group of advanced heart failure patients with a very limited prognosis. We therefore believe that an improved exercise capacity at 3 months follow-up can be seen as a clinically relevant success in this cohort. In contrast to the significant improvement in oxygen uptake, there was no improvement in any other CPET-related outcomes. This is especially remarkable for the VE/VCO_2 slope (39 ± 9 at baseline, 38 ± 7 at 3 months follow-up, $P = 0.62$), which has shown to be a prognostic parameter for RV function.[27] However, VE/VCO_2 slope has been measured as a submaximal parameter in this study (RER < 1.0). The prognostic value of VE/VCO_2 slope in this setting is controversial, and measuring VE/VCO_2 slope from start to maximum effort might therefore have shown different results.[28–30]

It should also be discussed that cardiac biomarkers did not show any significant change following transcatheter direct tricuspid leaflet repair. This finding is in contrast with the results of recent larger prospective studies[9,22] and could therefore be explained by the small sample size of this study.

Limitations

This investigation is a single-centre, retrospective study in a small number of patients. Due to the low number of cases, the statistically evaluation performed in this analysis must be interpreted with caution and a conclusion to larger cohorts cannot be drawn. There was no control group. Long-time follow-up data are missing. However, the study is hypothesis generating and could pave the way for future prospective assessment of functional capacity following transcatheter tricuspid valve repair.

Conclusions

Severe or greater TR is of prognostic relevance in heart failure patients. Novel interventional treatment options have merged. In a retrospective study in 11 patients, we could demonstrate improvement of VO_2 max following interventional direct leaflet repair in TR with the PASCAL Ace device. Our results are hypothesis generating and demand further evaluation in a prospective trial.

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Conflict of interest

None.

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