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ORIGINAL INVESTIGATIONS

Hemodynamic Assessment in Takotsubo Syndrome

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ABSTRACT

BACKGROUND Takotsubo syndrome (TTS) is a reversible form of heart failure with incompletely understood pathophysiology.

OBJECTIVES This study analyzed altered cardiac hemodynamics during TTS to elucidate underlying disease mechanisms.

METHODS Left ventricular (LV) pressure-volume loops were recorded in 24 consecutive patients with TTS and a control population of 20 participants without cardiovascular diseases.

RESULTS TTS was associated with impaired LV contractility (end-systolic elastance 1.74 mm Hg/mL vs 2.35 mm Hg/mL [$P = 0.024$]; maximal rate of change in systolic pressure over time 1,533 mm Hg/s vs 1,763 mm Hg/s [$P = 0.031$]; end-systolic volume at a pressure of 150 mm Hg, 77.3 mL vs 46.4 mL [$P = 0.002$]); and a shortened systolic period (286 ms vs 343 ms [$P < 0.001$]). In response, the pressure-volume diagram was shifted rightward with significantly increased LV end-diastolic ($P = 0.031$) and end-systolic ($P < 0.001$) volumes, which preserved LV stroke volume ($P = 0.370$) despite a lower LV ejection fraction ($P < 0.001$). Diastolic function was characterized by prolonged active relaxation (relaxation constant 69.5 ms vs 45.9 ms [$P < 0.001$]; minimal rate of change in diastolic pressure -1,457 mm Hg/s vs -2,192 mm Hg/s [$P < 0.001$]), whereas diastolic stiffness (1/compliance) was not affected during TTS (end-diastolic volume at a pressure of 15 mm Hg, 96.7 mL vs 109.0 mL [$P = 0.942$]). Mechanical efficiency was significantly reduced in TTS ($P < 0.001$) considering reduced stroke work ($P = 0.001$), increased potential energy ($P = 0.036$), and a similar total pressure-volume area compared with that of control subjects ($P = 0.357$).

CONCLUSIONS TTS is characterized by reduced cardiac contractility, a shortened systolic period, inefficient energetics, and prolonged active relaxation but unaltered diastolic passive stiffness. These findings may suggest decreased phosphorylation of myofilament proteins, which represents a potential therapeutic target in TTS. (Optimized Characterization of Takotsubo Syndrome by Obtaining Pressure Volume Loops [OCTOPUS]; NCT03726528) (J Am Coll Cardiol 2023;81:1979-1991) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ATP = adenosine triphosphate

ß = stiffness coefficient

CaMK II = Ca^{2+}/calmodulin-dependent protein kinase II

CMR = cardiac magnetic resonance

cMyBP-C = cardiac myosin-binding protein-C

dP/dt_{max} = maximal rate of change in systolic pressure over time

$-dP/dt_{min}$ = minimal rate of change in pressure over time

E_a = effective arterial elastance

EDP = end-diastolic pressure

EDPVR = end-diastolic pressure-volume relationship

EDV = end-diastolic volume

E_{es} = end-systolic elastance

ESP = end-systolic pressure

ESPVR = end-systolic pressure-volume relationship

ESV = end-systolic volume

k = fitting constant

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEDV15 = left ventricular end-diastolic volume at a pressure of 15 mm Hg

LVESP = left ventricular end-systolic pressure

LVESV150 = left ventricular end-systolic volume at a pressure of 150 mm Hg

PV = pressure-volume

TTS = Takotsubo syndrome

V_o = volume-axis intercept of the end-systolic pressure-volume relationship

Takotsubo syndrome (TTS) is a form of acute heart failure related to a distinctive pattern of regional ventricular contraction irregularities that result in characteristic end-systolic ballooning patterns.[1] The clinical features of TTS, which mimic acute coronary syndrome, and its prognostic implications with a considerable risk of acute cardiovascular complications and substantial long-term mortality rates have been well described in numerous scientific publications since its first description in Japan 3 decades ago.[2-5] The underlying pathophysiology of TTS, however, is still unclear and an ongoing matter of debate. A key role of sympathetic overdrive and excessive release of catecholamines is the most persistent theory considering the stressful triggers that precede the majority of TTS episodes. In addition, a genetic basis has been postulated,[6,7] and microvascular dysfunction and inflammation seem to play an important role, albeit the cause-effect relationship remains unknown.[1,8] Enhanced beta-adrenergic signaling and a higher sensitivity to catecholamine-induced toxicity have been suggested as potential mechanisms at the cellular level.[7] However, past scientific efforts did not lead to a real breakthrough in terms of the underlying mechanisms of TTS, and the lack of reliable TTS models that translate to humans impedes mechanistic experimental studies. Therefore, an intense focus on cardiovascular hemodynamics during TTS seems to be an appropriate approach to gain further insights and establish the groundwork for focused molecular and cellular research.

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Invasive tracing of pressure-volume (PV) relations is the gold standard for direct, real-time assessment of systolic and diastolic cardiac function independent of loading conditions.[9] In addition, PV loops provide in-depth information regarding ventricular-arterial coupling and cardiac energetics and efficiency. These parameters comprise a considerable amount of information on cardiac performance and help to advance our understanding of cardiac physiology and its pathophysiological role in various conditions. The aim of the OCTOPUS (Optimized Characterization of Takotsubo Syndrome by Obtaining Pressure Volume Loops; NCT03726528) study was to comprehensively analyze myocardial mechanics during TTS and subsequently make conclusions regarding potential underlying mechanisms of the disease.

METHODS

PATIENT COHORT. The OCTOPUS study was prospectively conducted between October 2018 and May 2022 at University Heart Center Lübeck, Germany, and included 24 patients with TTS. Study inclusion required a definite diagnosis of TTS according to European consensus criteria, which include the following: 1) transient regional left ventricular (LV) wall motion abnormalities usually extending beyond a single epicardial vascular distribution; 2) the absence of a culprit atherosclerotic coronary artery disease or other pathologic conditions to explain the pattern of temporary LV dysfunction; 3) new and reversible electrocardiographic abnormalities; 4) significantly elevated serum natriuretic peptides (N-terminal pro-B-type natriuretic peptide) but a relatively small elevation in cardiac troponin levels; and 5) recovery of ventricular systolic function on cardiac imaging at follow-up.[10] Transthoracic echocardiography was performed in all patients at acute presentation and at the 6-month follow-up to confirm complete recovery of systolic LV function. Moreover, patients without contraindications underwent cardiac magnetic resonance (CMR) imaging during the acute phase of the disease for diagnosis confirmation and exclusion of important differential diagnoses (eg, myocardial infarction with spontaneous lysis of thrombus or myocarditis).[11] Other inclusion criteria were sinus rhythm during hemodynamic assessment, age ≥18 years, and written informed consent for study participation. The main exclusion criteria were pronounced bundle branch block or rhythm disorders during invasive assessment (eg, premature ventricular contraction), cardiogenic shock, signs of another underlying condition on CMR imaging, persistent LV contraction abnormalities at follow-up, pregnancy, and participation in another trial. Severe mitral regurgitation or obstruction of the LV outflow tract as potential confounders of the hemodynamic conditions were excluded in all participants in the TTS group.

The control group consisted of 20 subjects without heart disease who underwent invasive assessment of PV relations using the same standardized protocol as in the TTS group. Patients with a clinical indication for coronary angiography (eg, stable angina pectoris, dyspnea) qualified as active comparators in the control group after the exclusion of relevant cardiovascular disorders (eg, coronary artery disease, valvular

TABLE 1 Baseline Characteristics

	Control (n = 20)	TTS (n = 24)	*P* Value
Age, y	57.2 ± 6.8	72.1 ± 9.5	**<0.001**
Female	10 (50.0)	23 (95.8)	**<0.001**
Cardiovascular risk factors			
Hypertension	11 (55.0)	15 (62.5)	0.614
Diabetes mellitus	3 (15.0)	3 (12.5)	0.810
Hypercholesterolemia	11 (55.0)	16 (66.7)	0.429
Current smoking	10 (50.0)	8 (33.3)	0.263
Body mass index, kg/m^2	27.2 (23.3-32.3)	21.7 (19.7-25.9)	**0.001**
Comorbidity			
Coronary artery disease	0 (0.0)	2 (8.3)	0.186
Atrial fibrillation	0 (0.0)	7 (29.2)	**0.008**
Malignancy	0 (0.0)	3 (12.5)	0.101
Pulmonary disease	8 (40.0)	8 (33.3)	0.647
Neurologic disorder	2 (10.0)	4 (16.7)	0.521
Psychiatric disorder	4 (20.0)	4 (16.7)	0.775
Stressful trigger	-	14 (58.3)	
Physical	-	7 (29.2)	
Emotional	-	7 (29.2)	
Clinical presentation			
Chest pain	-	18 (75.0)	
Dyspnea	-	6 (25.0)	
Killip class at admission			
I	-	22 (91.7)	
II	-	1 (4.2)	
III	-	1 (4.2)	
IV	-	0 (0.0)	
ST-segment changes	-	10 (41.7)	
Ballooning pattern			
Apical	-	16 (66.7)	
Midventricular	-	8 (33.3)	
Troponin T at admission, ng/L	-	236 (121-345)	
NT-proBNP at admission, ng/L	-	3,713 (2,203-5,981)	
Cardiac magnetic resonance			
LVEDV, mL	-	115.4 ± 29.5	
LVESV, mL	-	59.9 ± 21.6	
Stroke volume, mL	-	55.5 ± 17.0	
LVEF, %	-	48.8 ± 10.5	
Myocardial edema	-	12/16 (75)	
Late gadolinium enhancement	-	0/16 (0)	
Pericardial effusion	-	1/16 (6.3)	
Pleural effusion	-	1/16 (6.3)	
Right ventricular involvement	-	2/16 (12.5)	
In-hospital outcome			
Death	-	0 (0.0)	
Pulmonary edema	-	1 (4.2)	
Cardiogenic shock	-	0 (0.0)	

Continued in the next column

TABLE 1 Continued

	Control (n = 20)	TTS (n = 24)	*P* Value
Discharge medication			
Aspirin	3 (15.0)	8 (33.3)	0.162
Dual antiplatelet therapy	0 (0.0)	1 (4.2)	0.356
Oral anticoagulation	0 (0.0)	9 (37.5)	**0.002**
ACE inhibitor or ARB	9 (45.0)	23 (95.8)	**<0.001**
Beta-blocker	7 (35.0)	24 (100)	**<0.001**
Aldosterone antagonist	0 (0.0)	6 (25.0)	**0.016**
Diuretic agent	0 (0.0)	16 (66.7)[a]	**<0.001**
Statin	10 (50.0)	16 (66.7)	0.263

Values are mean ± SD, n (%), or median (IQR). *P* values in **bold** indicate a significant difference between study groups. No corrections for multiple testing were applied. [a]Preexisting thiazide diuretic as part of the antihypertensive therapy (n = 8); new thiazide diuretic to optimize hypertension control (n = 2); newly administered loop diuretic (n = 6).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TTS = Takotsubo syndrome.

heart disease, heart failure with reduced or preserved ejection fraction, pulmonary hypertension, heart rhythm disease). Furthermore, study inclusion required sinus rhythm during invasive measurements, an age of 18 years or older, written informed consent, and the exclusion of pregnancy or severe comorbidities with limited life expectancy <12 months. The in-depth evaluation of subjects in the control group with thorough exclusion of cardiovascular disorders ensured normal hemodynamic conditions as a basis to reveal pathologies in the TTS group.

The study complied with the principles of the Declaration of Helsinki and was approved by the local ethics committee at the University of Lübeck (Lübeck, Germany). Written informed consent was obtained from all study participants. The data supporting the findings of this study are available from the corresponding author on reasonable request.

CARDIAC CATHETERIZATION PROTOCOL. A standard coronary angiography and left ventriculography were performed via right radial or femoral artery access. Patients with a characteristic Takotsubo-like contraction pattern that was not explained by an epicardial coronary culprit lesion (TTS group) or patients without an evident cardiac disorder (control group) were included in the study and underwent further invasive assessment of PV relations. A 7-F conductance catheter with 8 mm spacing between the electrodes (CD Leycom) was retrogradely advanced into the left ventricle under fluoroscopic guidance and connected to a dedicated PV signal processor (Inca, CD Leycom). The segmental volume signals and PV loops were visually assessed in terms of angular shape, counterclockwise composition, and absence of twists as inclusion criteria for PV analysis. The PV catheter was repositioned in cases of <4 analyzable

segments or unstable signal quality. After ensuring a stable position of the catheter in the LV apex without inducing premature ventricular contraction, LV volume, LV pressure, and the electrocardiogram were simultaneously recorded, as previously described.[12,13] A data set was considered representative in case of high-quality PV loops of at least 15 consecutive heartbeats.

PV ANALYSES. A dedicated software, CircLab version 2020 (CircLab), was used to analyze the acquired raw data.[14] Single incorrect loops were excluded after visual beat-by-beat inspection, and the correct detection of end-systole and end-diastole was reviewed by manual check with the electrocardiogram. Volume calibration was performed with the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and stroke volume derived from left ventriculography.[13] Advanced PV analyses included systolic function, diastolic function, energetics, and ventricular-arterial coupling.

Systolic LV function. The maximal rate of change in systolic pressure over time (ie, dP/dt_{max}) is described as a marker of load dependent contractility. The end-systolic pressure-volume relationship (ESPVR) was determined by single-beat estimation.[14,15] A straight line between the calculated isovolumetric pressure maximum at a given preload (EDV) was connected with the measured left ventricular end-systolic pressure (ESP) and LVESV point of the corresponding single beat. The ESPVR is characterized by its slope (end-systolic elastance [E_{es}]) and volume-axis intercept (V_0) fitting the equation left ventricular end-systolic pressure (LVESP) = $E_{es} \times (LVESV - V_0)$.[14,15] Because both parameters of the ESPVR (E_{es} and V_0) have to be considered when defining contractility, the LVESV at a predefined LVESP of 150 mm Hg (LVESV150) was calculated as an integration of both slope and intercept: (150 mm Hg $- Y_0)/E_{es}$), where Y_0 is the intercept with the pressure-axis.[16] The time-varying elastance technique was used to determine the development of LV contractility. At each time point, the instantaneous elastance E(t) was assessed by connecting V_0 with the specific point of the PV loop: $E(t) = P(t)/[V(t) - V_0]$. Elastance-time curves were obtained for each beat by plotting instantaneous elastance vs time.[17] Maximal elastance (= E_{es}) as the peak of this curve and time to E_{es} indicating the duration of the systolic period were obtained to reflect the LV mode of action.[18] Peak power index is provided as another marker of cardiac contractility, calculated by LVESP $\times$ peak ejection rate/LVEDV.

Diastolic LV function. The end-diastolic pressure-volume relationship (EDPVR) was assessed as a measure of diastolic stiffness with a single-beat approach.[16,19] Diastolic PV coordinates at the lower boundary of the PV loops formed the EDPVR curve by fitting the equation $LVEDP = k \times e^{ß \times LVEDV}$, where ß is the chamber stiffness coefficient and k is the fitting constant. Again, both parameters of the EDPVR (ß and k) have to be considered when defining diastolic stiffness, which can be achieved by calculating the LVEDV at a predefined LVEDP of 15 mm Hg: $LVEDV15 = Ln(15/k)/b$.[16] Thus, LVEDV15 incorporates the fitting and stiffness constants. In the pressure time diagram, the pressure decrease during isovolumic relaxation can be described by the relationship $P(t) = P_0 \times e^{-t/\tau}$ where P_0 is LV pressure at maximal $-dP/dt_{min}$ (the point at which the rate of LV pressure decline is maximal), t is the time after onset of relaxation, and τ is the time constant of isovolumetric relaxation according to Weiss et al.[20] Peak filling rate describes the maximal rate in volume increase during diastole in the left ventricle.

Ventricular-arterial coupling and energetics. The effective arterial elastance (E_a), indicating LV afterload, was calculated as the ratio between LVESP and stroke volume. Ventricular-arterial coupling was assessed as E_a/E_{es}.[9] LV energetics were characterized by the total PV area, which is the sum of stroke work or kinetic energy determined by the area within the PV loop and the residual potential energy, which can be derived from the triangle bordered by the ESPVR, the volume axis, and the PV loop.[17,21] Mechanical efficiency was calculated as stroke work divided by total PV area.

An operator (J.-C.R.) with extensive experience in hemodynamic analysis and without knowledge of the patient's clinical characteristics analyzed the PV data.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD if normally distributed or as median (IQR) if nonnormally distributed. The Shapiro-Wilk test was used to test normality of data. Categorical variables are presented as frequencies and percentages. Comparisons between the TTS group and the control group were made by using the chi-square test for categorical variables. Continuous data were compared with Student's t-test or the nonparametric Mann-Whitney U test as appropriate. The duration of the systolic period was additionally assessed in the subgroup of patients with a normal heart rate, defined as <95 beats/min.

Statistical analyses were performed with SPSS version 27.0 (IBM SPSS Statistics, IBM Corporation) and MedCalc version 19.6.4 (MedCalc Software). A 2-tailed P value <0.05 was considered statistically significant. Of note, P values presented in this report

TABLE 2 Hemodynamic Measurements

	Control (n = 20)	TTS (n = 24)	*P* Value
Basic hemodynamics			
Heart rate, beats/min	73.4 ± 10.6	83.7 ± 16.7	**0.017**
LVEDV, mL	108 (89 to 129)	125 (104 to 171)	**0.031**
LVEDV index, mL/m^2	54.5 (44.7 to 64.6)	79.4 (65.3 to 94.6)	**<0.001**
LVESV, mL	44 (39 to 46)	72 (52 to 93)	**<0.001**
LVESV index, mL/m^2	21.5 (19.5 to 23.6)	42.2 (33.4 to 50.3)	**<0.001**
LVSV, mL	65 (54 to 87)	62 (49 to 79)	0.370
LVSV index, mL/m^2	34.1 (27.1 to 44.6)	37.9 (30.1 to 44.2)	0.768
LVEF, %	61.8 ± 6.6	47.8 ± 9.9	**<0.001**
Systolic function			
LVESP, mm Hg	127.8 ± 20.0	125.7 ± 21.9	0.748
E_{es}, mm Hg/mL	2.35 (1.80 to 3.40)	1.74 (0.98 to 2.59)	**0.024**
V_O, mL	-12.5 ± 26.6	-16.1 ± 33.4	0.693
dP/dt_{max}, mm Hg/s	1,763.4 ± 326.7	1,533.0 ± 356.6	**0.031**
LVESV150, mL	46.4 (39.9 to 62.3)	77.3 (51.1 to 119.0)	**0.002**
Peak power index, mm Hg/s	-737.5 (-1,668.6 to -452.1)	-1,141.0 (-1,409.7 to -887.4)	0.109
Systolic time, ms	342.8 ± 26.1	286.0 ± 34.4	**<0.001**
Diastolic function			
LVEDP, mm Hg	13.5 ± 3.4	19.2 ± 4.8	**<0.001**
Tau, ms	45.9 ± 10.3	69.5 ± 14.9	**<0.001**
$-dP/dt_{min}$, mm Hg/s	-2,191.5 (-2,628.0 to -1,754.3)	-1457.0 (-1,556.0 to -1,169.3)	**<0.001**
Peak filling rate, mL/s	870.5 (786.3 to 1,633.8)	863.0 (653.5 to 1,470.5)	0.258
ß, 1/mL	0.027 (0.021 to 0.034)	0.015 (0.011 to 0.030)	**0.021**
k, mm Hg	0.73 (0.44 to 1.43)	2.54 (0.88 to 4.10)	**0.011**
LVEDV15, mL	109.0 (84.7 to 130.8)	96.7 (79.6 to 162.1)	0.942
Ventricular-arterial coupling			
E_a, mm Hg/mL	1.82 (1.55 to 2.15)	2.14 (1.63 to 2.51)	0.258
E_a/E_{es}	0.76 (0.57 to 0.96)	1.22 (0.97 to 1.44)	**<0.001**
Energetics			
Stroke work, mm Hg × mL	7,902.9 ± 2657.1	5,378.5 ± 1,884.1	**0.001**
Potential energy, mm Hg × mL	2,936 (2,177 to 3,964)	4741 (2,782 to 6,450)	**0.036**
Total pressure volume area, mm Hg × mL	11,454.0 ± 4,153.9	10,303.2 ± 3,993.1	0.357
Mechanical efficiency	0.701 ± 0.072	0.536 ± 0.101	**<0.001**

Values are mean ± SD or median (IQR). *P* values in **bold** indicate a significant difference between study groups. No corrections for multiple testing were applied.

ß = stiffness coefficient; dP/dt_{max} = maximal rate of change in systolic pressure over time; dP/dt_{min} = minimal rate of change in pressure over time; E_a = effective arterial elastance; E_{es} = end-systolic elastance; *k* = fitting constant; LVEDP = left ventricular end-diastolic pressure; LVEDV15 = left ventricular end-diastolic volume at a pressure of 15 mm Hg; LVESP = left ventricular end-systolic pressure; LVESV150 = left ventricular end-systolic volume at a pressure of 150 mm Hg; LVSV = left ventricular stroke volume; V_O = volume-axis intercept of the end-systolic pressure-volume relationship; other abbreviations as in Table 1.

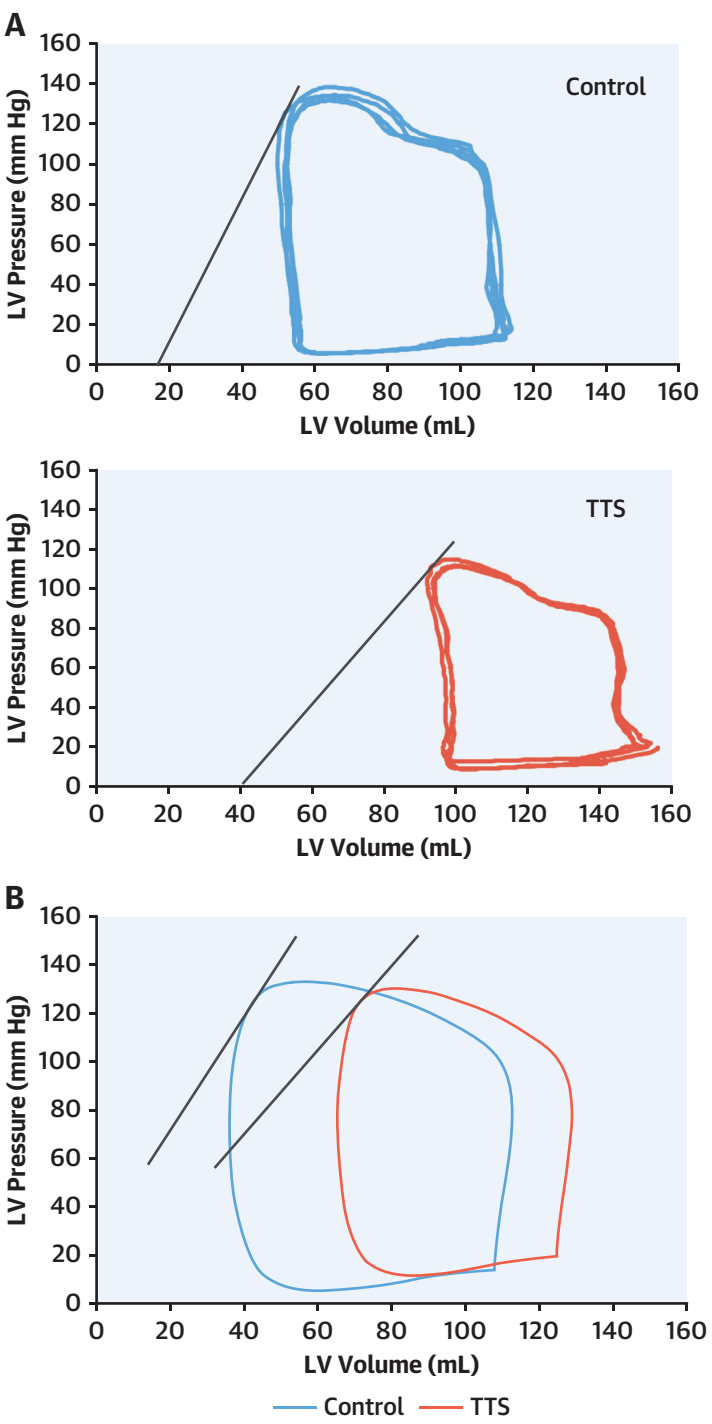
have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible.

RESULTS

CLINICAL AND DEMOGRAPHIC DATA. During the study period, 36 patients with suspected TTS were evaluated for inclusion in the OCTOPUS trial. Of these, 11 patients were excluded because of cardiogenic shock (n = 3), atrial fibrillation during cardiac catheterization (n = 6), and refusal of consent for participation (n = 2). A total of 25 patients were included in the study and underwent comprehensive hemodynamic assessment with PV loop recordings. One patient was excluded post hoc because of persistent wall motion abnormalities and detection of myocardial scar tissue on CMR, resulting in a final study population of 24 patients with confirmed TTS. Hemodynamic assessment was performed within 24 hours after hospital admission in the majority of patients (79%). The median time from symptom onset to PV loop recordings was 1 day (IQR: 1-2 days).

Baseline clinical characteristics are presented in Table 1 and reveal a typical TTS population of predominantly postmenopausal women with a moderate cardiovascular risk profile and age-appropriate comorbidity. A preceding stressful trigger was evident in 58% of patients; the ballooning pattern was apical in two-thirds and midventricular in one-third of the population. CMR could not be performed in 6 patients because of contraindications (metallic implants,

FIGURE 1 PV Loops



Representative pressure–volume (PV) loops of a participant in the control group and a patient with Takotsubo syndrome (TTS) **(A)** and average PV loops of the respective study cohorts **(B)**. TTS was characterized by a rightward shift in the PV diagram with elevated left ventricular (LV) end-diastolic and end-systolic volumes but a preserved LV stroke volume. The end-systolic PV relationship was flattened in patients with TTS, which illustrates impaired cardiac contractility and increased potential energy with overall inefficient energetics.

n = 3; claustrophobia, n = 3), and 2 patients terminated the scan prematurely. Therefore, complete CMR data sets were available in 16 patients with TTS (67%) with a median time from hospital admission to image acquisition of 3 days (IQR: 2-4 days). The results are reported in Table 1 and reflect typical findings in TTS, with myocardial edema in 75% of patients and absence of scar tissue. The control group included male and female participants in equal shares. The cohort was significantly younger compared with patients with TTS ($P < 0.001$) but exhibited similar cardiovascular risk factors, which was the primary indication for coronary angiography. As expected, the prescribed discharge medication differed significantly between the study groups.

LV VOLUMES AND EJECTION FRACTION. The results of comprehensive LV hemodynamic assessment are summarized in Table 2. Compared with control subjects, patients with TTS exhibited a rightward shift in the PV diagram (Figure 1) characterized by a significantly increased LVEDV ($P = 0.031$) and LVESV ($P < 0.001$) but a preserved LV stroke volume ($P = 0.370$) (Figures 2A-2C). These findings were persistent after correction for body surface area. Consequently, LV ejection fraction was significantly reduced during TTS ($P < 0.001$) (Figure 2D), whereas heart rate was higher than in the control group ($P = 0.017$).

SYSTOLIC LV FUNCTION. A significantly reduced E_{es} ($P = 0.024$) and dP/dt_{max} ($P = 0.031$), as well as an increased LVESV150 ($P = 0.002$), underscore the pronounced impairment of cardiac contractility in patients with TTS beyond LV ejection fraction (Table 2, Figures 3A to 3C). Systolic time was significantly shorter in patients with TTS compared with the control group ($P < 0.001$) (Figure 3D). Because the duration of systole depends on heart rate, which differed significantly between the study groups, systolic time was also evaluated in the subgroup of patients with a normal heart rate (patients with TTS, n = 17; control subjects, n = 19). In this analysis, LV systolic time remained significantly shorter in the TTS group compared with the control group (299 ± 32 ms vs 344 ± 26 ms; $P < 0.001$) despite balanced heart rates (75.5 ± 11.8 beats/min vs 72.1 ± 9.3 beats/min; $P = 0.353$).

DIASTOLIC LV FUNCTION. In accordance with the increased LVEDV, LVEDP was significantly elevated in patients with TTS compared with control subjects ($P < 0.001$) (Table 2, Figure 4A). Myocardial relaxation was significantly prolonged during TTS, indicated by the increased relaxation time constant tau ($P < 0.001$) (Figure 4B) and $-dP/dt_{min}$ ($P < 0.001$) (Figure 4C). In

contrast, diastolic passive stiffness was unaltered in patients with TTS, because LVEDV15 (as the combined parameter of LV compliance that incorporates both the stiffness constant ß and the fitting constant *k*) did not differ significantly between groups ($P = 0.942$) (Figure 4D).

VENTRICULAR-ARTERIAL COUPLING AND LV ENERGETICS. Although E_a as a measure of LV afterload did not differ between patients with TTS and control subjects ($P = 0.258$), the coupling ratio of E_a/E_{es} was significantly elevated during TTS ($P < 0.001$) (Table 2). This result was driven by reduced cardiac contractility (E_{es}), which favors a waste of mechanical energy; in accordance, stroke work (= kinetic energy) was significantly reduced in patients with TTS ($P = 0.001$) (Figure 5A), whereas potential energy increased markedly ($P = 0.036$) (Figure 5B). The total pressure volume area did not differ between the study groups ($P = 0.357$). Consequently, mechanical efficiency was significantly reduced during TTS ($P < 0.001$).

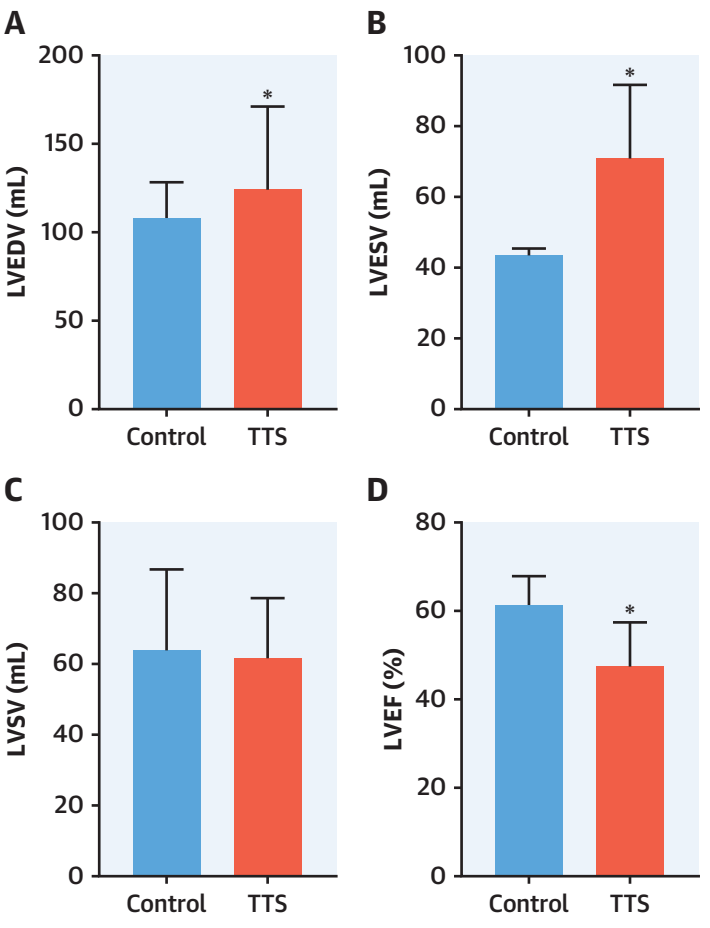
DISCUSSION

To the best of our knowledge, this study provides the first comprehensive hemodynamic analysis in patients with TTS using invasive tracing of PV loops. The main results are summarized in the Central Illustration. TTS is associated with a severely impaired cardiac contractility and a shortened systolic period. In response, the Frank-Starling mechanism is used excessively to balance this state by increasing LVEDV, compensating for the increased LVESV and thereby preserving the stroke volume. Diastolic function is characterized by prolonged active relaxation but unaltered passive elastic properties. The analysis of myocardial energetics revealed an inefficient system with increased potential and decreased kinetic energy (stroke work).

HEMODYNAMIC FEATURES OF TTS. Currently available evidence regarding invasive hemodynamics and cardiac mechanics in TTS are restricted to a single retrospective analysis that used standard fluid-filled catheters.[22] In contrast, our prospective study is based on direct recordings of PV loops with a dedicated conductance catheter placed in the left ventricle, which is the gold standard for invasive hemodynamic assessment and considerably expands and clarifies previous findings. Both investigations consistently objectify the profound impairment of ventricular contractility during TTS by reporting a decreased E_{es} and reduced stroke work. Our study adds additional markers of altered systolic properties (eg, dP/dt_{max}, LVESV150) and reveals a significantly shortened systolic period in patients with TTS. Of note, systolic time is independently associated with outcome in patients with heart failure[23] and might play an important role in pathophysiological considerations derived from hemodynamic changes in TTS.

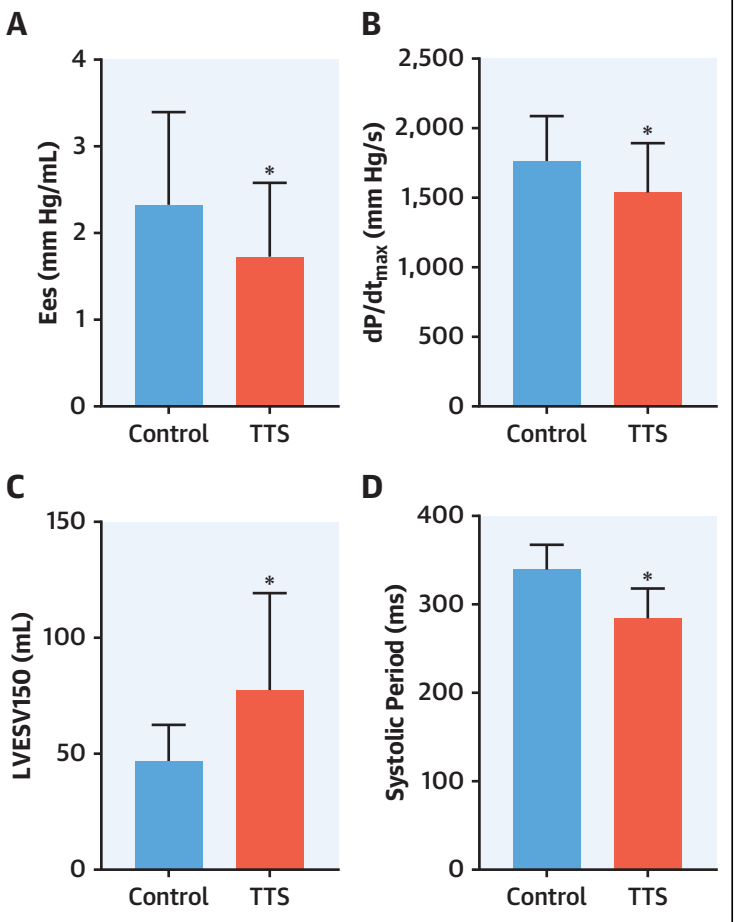
In-depth evaluation of myocardial energetics during TTS showed an increase in elastic potential energy, which is the remaining energy stored in the myofilaments at end-systole that is not converted into external stroke work and dissipates during

FIGURE 2 LV Volumes and EF



Compared with control subjects, patients with TTS exhibited a significantly elevated left ventricular end-diastolic volume (LVEDV) **(A)** and left ventricular end-systolic volume (LVESV) **(B)** but a preserved left ventricular stroke volume (LVSV) **(C)**, resulting in a markedly decreased left ventricular ejection fraction (LVEF) **(D)**. Data are presented as mean ± SD or median (IQR); no corrections for multiple testing were applied, *$P < 0.05$. Abbreviations as in Figure 1.

FIGURE 3 Systolic LV Function



TTS was associated with a substantial impairment of cardiac contractility, as illustrated by a significantly reduced end-systolic elastance (E_{es}) **(A)** and maximal rate of change in systolic pressure over time (dP/dt_{max}) **(B)**, as well as an increased left ventricular end-systolic volume at a pressure of 150 mm Hg (LVESV150) **(C)**. **(D)** The systolic period was significantly reduced in TTS compared with control subjects. Data are presented as mean ± SD or median (IQR); no corrections for multiple testing were applied, $*P < 0.05$. Abbreviations as in Figure 1.

relaxation.[9] In view of a similar total mechanical energy in both groups, the utilization of myocardial work is inefficient in TTS, with a lot of wasted energy during ventricular contraction and relaxation. Furthermore, there is a mismatch between ventricular and vascular properties, again mainly related to reduced ventricular contractility. The impact of afterload in the arterial circulation on the increased ventricular-arterial coupling ratio differed between the current study and previous findings. Although our analysis revealed similar E_a in both cohorts, previously published data suggest an increased arterial stiffness in TTS as an attempt to maintain arterial pressure to compensate for ventricular dysfunction.[22] However, there is consensus that a main mechanism to balance the acute hemodynamic alterations in TTS is the increase in LVEDV to preserve LV stroke volume and cardiac output. In contrast, the interpretation of diastolic dysfunction in TTS is to some extent fundamentally different. Several abnormal markers of LV stiffness in the presence of elevated LVEDP previously led to the assumption that increased stiffness causes diastolic dysfunction in patients with TTS.[22] Our data confirm a severely impaired diastolic function during TTS, but the advanced method of evaluation allowed for a detailed differentiation between active relaxation, which is energy dependent, and passive ventricular filling. The results indicate prolonged myocardial relaxation, whereas ventricular compliance was not affected by TTS. These findings are in accordance with the lack of structural myocardial injury in patients with TTS,[11] although ventricular compliance is a complex process with many influencing factors.

TRANSLATION INTO PATHOPHYSIOLOGY. Decoding the pathophysiology of TTS is a scientific challenge because it seems to integrate changes in the central nervous system (eg, sympathetic overdrive, catecholamine surge) and its downstream effects on the cardiovascular system.[24-26] Our study provides novel insights into the acute myocardial alterations and thereby suggests a potential therapeutic approach in patients with TTS. Cardiomyocyte failure, arrhythmias, and Ca^{2+} overload are hallmarks of TTS.[24] The toxic effects of catecholamines on the myocardium are characterized by a loss of their inotropic effects through beta-receptor downregulation and activation of inhibitory G proteins.[27] Accordingly, myocardial biopsy specimens exhibited sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) hypoactivity and dephosphorylated phospholamban as potential causes for contractile dysfunction and prolonged relaxation, which were particularly shown in our study.[28]

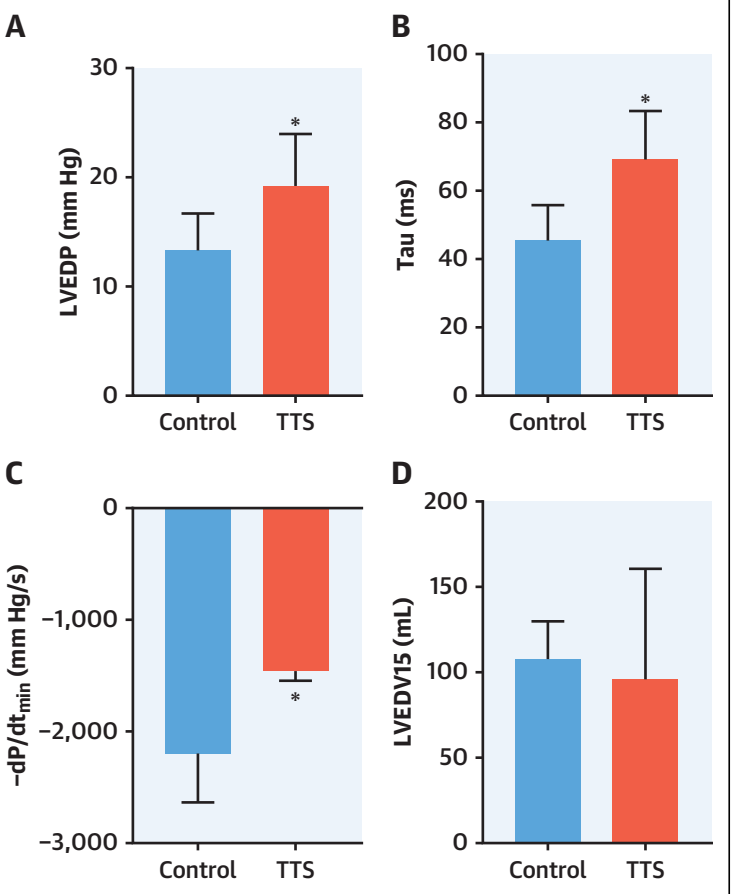
In addition, profiles of elastance-time curves provide further details about the underlying molecular mechanisms of different inotropic states of the heart.[15,18] Myofilament activators, Ca^{2+} sensitizers, and catecholamines affect time-dependent elastance curves in very characteristic but distinct ways.[18,29] Stimulation of beta-adrenoceptors enhances the steepness of the initial rise and fall of the elastance-

time curve and abbreviates the systolic period with an earlier peak (E_{es}). The adrenergic mode is promoted by activation of protein kinase A with a coordinated increase in Ca^{2+} transient but faster cytosolic Ca^{2+} decay (sarcoplasmic reticulum Ca^{2+} ATPase).[18,29] In contrast, myofilament activators (eg, omecamtiv mecarbil) and Ca^{2+} sensitizers (eg, levosimendan) increase E_{es} and prolong time to E_{es}, thereby extending the LV systolic period, likely accomplished by enhanced recruitment of strongly bound cross-bridges that delay dissociation of the actomyosin interaction.[18,30] Furthermore, the afterload-dependent increase in contractility (ie, the Anrep effect) showed striking similarities to myofilament activators with a prolonged systolic ejection period and E_{es}, which was mainly assigned to the enhanced phosphorylation of cardiac myosin-binding protein-C (cMyBP-C) by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII).[15] This was corroborated by the finding that animals exhibit a reduced elastance-time curve peak at higher afterload levels following CaMKII deletion.[15]

In light of these results, it is likely that decreased phosphorylation of myofilament proteins (eg, cMyBP-C) related to a hypoactivity of CaMKII partially accounts for the impaired contractility and altered elastance-time curve with a reduced E_{es} and shortened systolic period in TTS. By decreasing ejection time due to fewer actomyosin contacts (ie, fewer strongly bound cross-bridges), low phosphorylation of cMyBP-C is sufficient to minimize dP/dt_{max} and, by extension, peak E_{es}. This hypothesis is further strengthened by the myocardial energetics of patients with TTS, characterized by increased potential energy, decreased kinetic energy, and similar afterload compared with control subjects. Muscle maximal force generation decreases, ejection fraction drops, and bigger cavity filling volumes can be accommodated if strongly bound cross-bridge interactions are diminished (ie, myofilaments become less sensitive to Ca^{2+}).

TTS may therefore be treated with medications that lengthen the systole and improve contractility, such as levosimendan and/or omecamtiv mecarbil, possibly in combination with beta-blockers to protect against the intense adrenergic activation. Several studies have reported the use of levosimendan in TTS and suggest positive effects by accelerating recovery of ventricular function. However, prospective data are lacking, and, to the best of our knowledge, omecamtiv mecarbil has not been tested in TTS.[31]

FIGURE 4 Diastolic LV Function

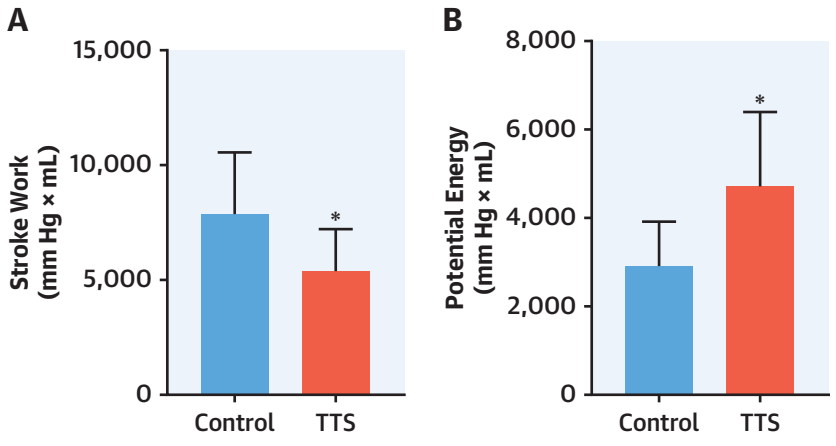


Patients with TTS exhibited a significantly elevated left ventricular end-diastolic pressure (LVEDP) **(A)** and prolonged active myocardial relaxation, which is illustrated by an increased relaxation constant tau **(B)** and minimal rate of change in pressure over time ($-dP/dt_{min}$) **(C)**. **(D)** Passive stiffness (myocardial compliance), in contrast, was not affected during TTS with a similar left ventricular end-diastolic volume at a pressure of 15 mm Hg (LVEDV15) in both groups. Data are presented as mean ± SD or median (IQR); no corrections for multiple testing were applied, $*P < 0.05$. Abbreviations as in Figure 1.

Therefore, more research, including myocardial biopsies, is necessary to corroborate this theory.

The impaired mechanical efficiency in TTS may also be related to cardiac metabolic dysregulation. The heart primarily utilizes fatty acids rather than glucose, amino acids, or ketones for energy regeneration under physiological conditions.[32] In heart failure, studies have shown a decreased phosphocreatine to adenosine triphosphate (ATP) ratio, indicating reduced cardiac energy recycling.[33] Investigations in TTS reported high levels of alanine,

FIGURE 5 LV Energetics



Stroke work (= kinetic energy) was significantly reduced in patients with TTS **(A)**, whereas potential energy increased markedly **(B)**. TTS was therefore associated with mechanical inefficiency considering a similar total PV area in both groups. Data are presented as mean ± SD or median (IQR); no corrections for multiple testing were applied, *$P < 0.05$. Abbreviations as in Figure 1.

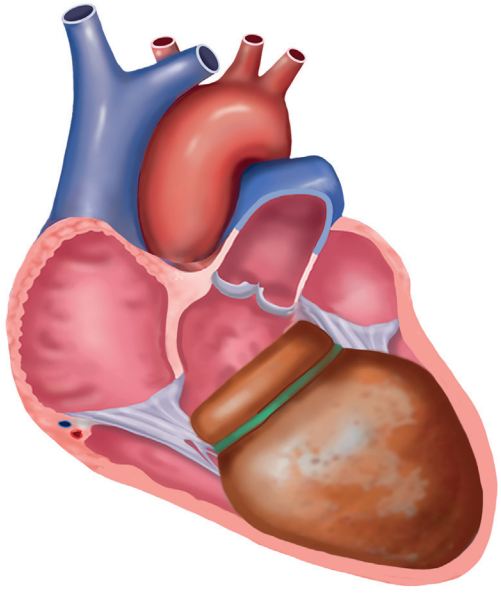
creatine, and acetate in the serum, suggesting reduced activity of the Krebs cycle and consequently reduced mitochondrial oxidative phosphorylation and ATP regeneration.[34,35] This energy mismatch correlates with a shift from fatty acid to glucose-driven oxidation, reducing reliance on oxygen availability to ensure ATP regeneration, and it is accompanied by increased intramyocardial lipid buildup and decreased mitochondrial absorption of long-chain fatty acids.[36-38] However, previous research does not consistently support this theory. Although animal studies showed increased glucose-driven oxidation in TTS, human studies reported a decline in myocardial glucose uptake and glycolytic rates with normal cardiac perfusion.[37,39] Furthermore, ketones are also considered as an alternative source of energy in TTS, with additional anti-inflammatory and antioxidant effects.[37,40,41] Ongoing metabolic dysregulation might also explain why patients with TTS continue to be symptomatic despite recovery of LV systolic function or experience recurrent events.

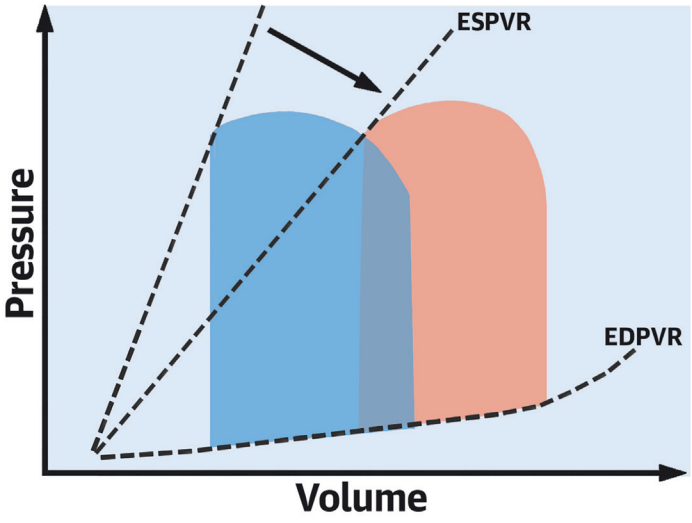
STUDY LIMITATIONS. This study is the first to provide detailed insights into altered hemodynamics during TTS by using invasive tracings of PV loops. The sample size is moderate and similar to comparable previous investigations. The population of patients with TTS is well characterized with thorough diagnostic work-up, including CMR imaging in the majority of cases but limited to stable patients in sinus rhythm. Hemodynamic conditions might diverge in unstable patients or in the presence of arrhythmias such as atrial fibrillation. The control group consisted of middle-aged subjects without apparent cardiovascular diseases but cannot be described as completely "healthy" considering comorbidity and risk factors. Finally, mechanistic considerations are hypothesis generating in the absence of definite proof on the molecular level and require validation in future studies, ideally including myocardial biopsies.

CONCLUSIONS

Acute hemodynamic changes in TTS are characterized by reduced cardiac contractility in the presence of a shortened systolic period, inefficient myocardial energetics, and prolonged active myocardial relaxation but unaltered diastolic passive stiffness. Translating these findings into pathophysiological considerations may suggest a decreased phosphorylation of myofilament proteins such as cMyBP-C, which constitutes a potential therapeutic target by using medications that lengthen the systolic period and improve contractility. This hypothesis, however, requires further validation in future trials.

CENTRAL ILLUSTRATION **Hemodynamics in Takotsubo Syndrome**





Cardiac Contractility ↓ | Systolic Time ↓

LVEDV ↑ | LVESV ↑ | LVSV ↔

LVEDP ↑ | Relaxation Time ↑ | Compliance ↔

Stroke Work ↓ | Potential Energy ↑ | Efficiency ↓

Stiermaier T, et al. J Am Coll Cardiol. 2023;81(20):1979–1991.

Takotsubo syndrome is associated with a severely impaired cardiac contractility and a shortened systolic period, which is balanced by increasing left ventricular end-diastolic volume (LVEDV) to preserve the left ventricular stroke volume (LVSV). Diastolic properties are characterized by prolonged active relaxation, but unaltered passive elastic properties and myocardial energetics reveal an inefficient system with increased potential and decreased kinetic energy (stroke work). EDPVR = end-diastolic pressure-volume relationship; ESPVR = end-systolic pressure-volume relationship; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVESV = left ventricular end-systolic volume.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Acute hemodynamic changes in TTS reflect impaired myocardial contractility, a shortened systolic period, inefficient myocardial energetics, and prolonged myocardial relaxation but unaltered passive diastolic stiffness.

TRANSLATIONAL OUTLOOK: Further research is needed to evaluate potential treatments that increase phosphorylation of myofilament proteins, lengthen the systolic period, and improve myocardial contractility in patients with TTS.

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KEY WORDS **hemodynamics, pathophysiology, Takotsubo syndrome**