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ORIGINAL ARTICLE
Heart failure

Impact of intra-aortic balloon counterpulsation on all-cause mortality among patients with Takotsubo syndrome complicated by cardiogenic shock: results from the German-Italian-Spanish (GEIST) registry

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Aims Takotsubo syndrome (TTS) is an acute and reversible left ventricular dysfunction and can be complicated by cardiogenic shock (CS). However, few data are available on optimal care in TTS complicated by CS. Aim of this study was to evaluate short- and long-term impact of intra-aortic balloon pumping (IABP) on mortality in this setting.

Methods and results In a multi-centre, international registry on TTS, 2248 consecutive patients were enrolled from 38 centres from Germany, Italy, and Spain. Of the 2248 patients, 212 (9.4%) experienced CS. Patients with CS had a higher prevalence of diabetes (27% vs. 19%), male sex (25% vs. 10%), and right ventricular involvement (10% vs. 5%) ($P < 0.01$ in all cases). Forty-three patients with CS (20% of 212) received IABP within 8 h (interquartile range 4–18) after admission. No differences in terms of age,

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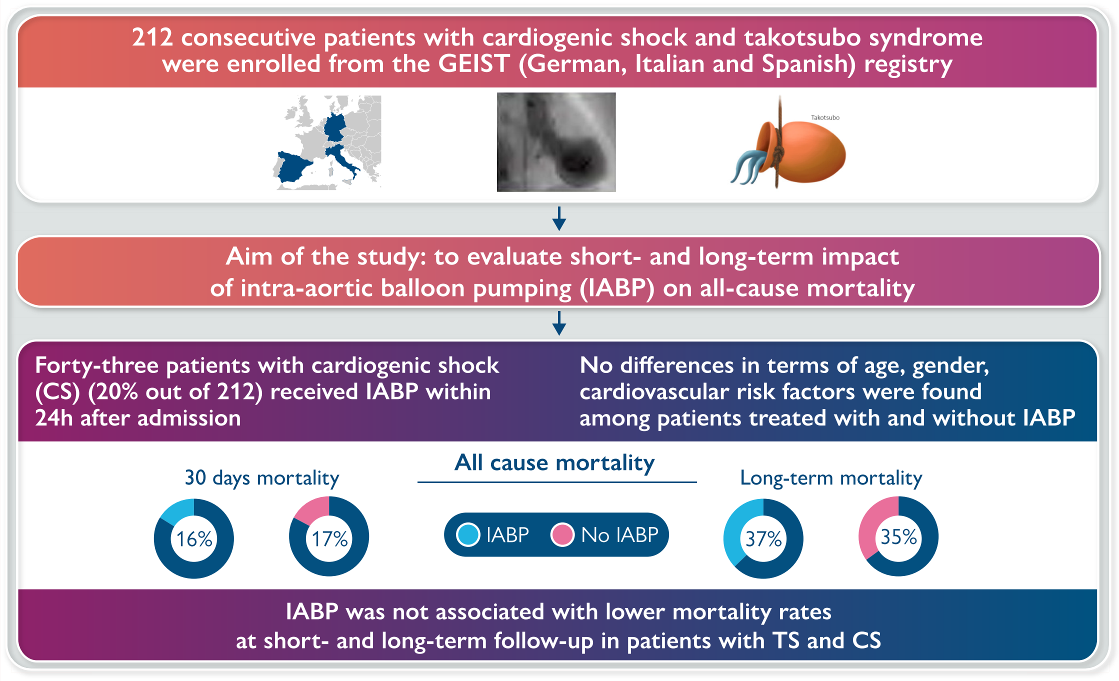
gender, cardiovascular risk factors, and admission left ventricular ejection fraction were found among patients with and without IABP. There were no significant differences in terms of 30-day mortality (16% vs. 17%, $P = 0.98$), length of hospitalization (18.9 vs. 16.7 days, $P = 0.51$), and need of invasive ventilation (35% vs. 41%, $P = 0.60$) among two groups: 30-day survival was not significantly different even after propensity score adjustment (log-rank $P = 0.73$). At 42-month follow-up, overall mortality in patients with CS and TTS was 35%, not significantly different between patients receiving IABP and not (37% vs. 35%, $P = 0.72$).

Conclusions In a large multi-centre observational registry, the use of IABP was not associated with lower mortality rates at short- and long-term follow-up in patients with TTS and CS.

Graphical Abstract



Mechanical support with intra-aortic balloon pumping (IABP) in patients with Takotsubo syndrome and cardiogenic shock was not associated with survival benefit at short- and long-term mortality.

Keywords Cardiogenic shock • GEIST • IABP • In-hospital complications • Intra-aortic balloon counter-pulsation • Stress cardiomyopathy • Takotsubo syndrome

Introduction

Takotsubo syndrome (TTS) is a reversible and transient left ventricular (LV) dysfunction,[1] featured by acute heart failure. Although considered as a benign disease, several studies showed that TTS is featured by high rates of in-hospital complications and not favourable long-term outcome.[2,3] The incidence of in-hospital complications (IHCs) is about 25%,[4] and these IHCs are mainly represented by several forms of acute heart failure including pulmonary oedema and cardiogenic shock (CS).[5,6] Incidence of CS in patients admitted with TTS ranges from 9.5% to 11.4%[7,8,9] and has been associated with poor outcome at short- and long-term follow-up. However, there is no standard therapy for CS in TTS. Several approaches have currently been proposed as mechanical support mainly with intra-aortic balloon counterpulsation (IABP),[10] levosimendan,[11] catecholamine infusion,[12] and short-acting β1-selective blocker (esmolol)[13] in case of LV outflow tract obstruction.

Mechanical support with IABP in case of CS may be potentially useful by reduction of afterload in left ventricular systole and increase of coronary blood flow during diastole.

However, the role of IABP in CS is still debated. Although for patients with acute myocardial infarction and CS, IABP has no effect on all-cause mortality,[14] in the context of acute-on-chronic heart failure complicated by cardiogenic shock IABP can provide potential benefit to those patient candidates for cardiac replacement therapies.[15]

Aim of this study was therefore to assess short- and long-term outcome in patients with CS and TTS treated with IABP in a large, international, multi-centre registry.

Methods

Study population

The study population included 212 consecutive patients with CS and TTS from a multi-centre-international registry (German, Italian, and Spanish Takotsubo registry, NCT 04361994) that has enrolled 2248 patients, involving 38 institutions from Germany, Italy, and Spain (*Figure 1*; Supplementary material online, *Table S1*).

Inclusion criteria

All patients with suspected diagnosis of TTS underwent coronary angiogram. The diagnosis of TTS was based on the position statement of the 2016 European Heart Failure Association.[16]

Clinical and echocardiographic examination

All patients underwent clinical examination, and baseline features like gender, age, medical history, and kind of stressors were recorded. All patients underwent two-dimensional Doppler echocardiogram examination at admission. The LV ejection fraction (LVEF) was calculated through the Simpson method using the two- and four- chamber view.[17] LV dysfunction patterns were classified as previously defined: apical ballooning, mid-ventricular ballooning, and basal ballooning.[18]

Cardiogenic shock management

Patients received the best available medical treatment according to current guidelines for CS.[19] Catecholaminergic inotropic agents were avoided, and fluid administration was performed according to echocardiographic evaluation of mitral and aortic valve and RV function.[20] According to operator choice, patients with CS underwent IABP implantation or not. The IABP was inserted within 8 h (interquartile range 4–18) after admission either before or immediately after coronary angiography, with the timing of the insertion at the discretion of the investigator. Support was initiated with the use of 1:1 ECG triggering (i.e. balloon inflation and deflation triggered by the R wave) and was maintained until there was sustained haemodynamic stabilization, defined as a systolic values of blood pressure higher than 90 mmHg for more than 30 min. Weaning from the pump was achieved through reduction of the trigger ratio.[21] No additional cardiac assistance device, other than IABP, was used for patients enrolled in this registry.

Heart failure management

All patients received standard therapy for acute heart failure mainly with diuretics and ventilatory support according to current guidelines.[22] No differences in terms of heart failure therapy were found over time and among centres.

Definition of outcome

The primary clinical endpoint was all cause mortality at 30 days and at long-term among patients with CS and TTS treated with mechanical support with IABP or not.

Definition of CS was as follows: systolic blood pressure less than 90 mmHg for more than 30 min and clinical signs of impaired organ perfusion and pulmonary congestion, with one of the following criteria: (i) cold skin and extremities; (ii) altered mental status; (iii) level of arterial lactate >2 mmoL/L; or (iv) oliguria (≤30 mL per hour).[23]

All patients gave a written informed consent for participation in the registry. The study received approval by an institutional review board and ethics committee in each centre (approval number 143/2019 of the ethics committee for the coordinating centre).

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD), and categorical variables were expressed as proportions; the Kolmogorov–Smirnov test was used to evaluate normal distribution of variables. Groups were compared with unpaired *t*-test or χ^2 test as required. Log-rank test and Kaplan–Meier plots were used to evaluate events survival freedom at short- and long-term follow-up.

Cox's regression analysis was used to identify predictors for mortality; relative risks (RRs) with 95% confidence intervals were calculated. Forward multivariable logistic regression analysis was used for correcting bias of principal confounders. Variables significant at univariate analysis ($P < 0.05$) were included in multivariate analysis.

A propensity-matched population was selected from overall population with CS after calculation of a propensity score for receiving IABP according to the following variables: age, gender, and LVEF. A nearest-neighbor 1:1 variable ratio, parallel, balanced propensity-matching model without replacement was made using caliper of width equal to 0.001 propensity score discordance. A *P*-value <0.05 was considered as statistically significant.

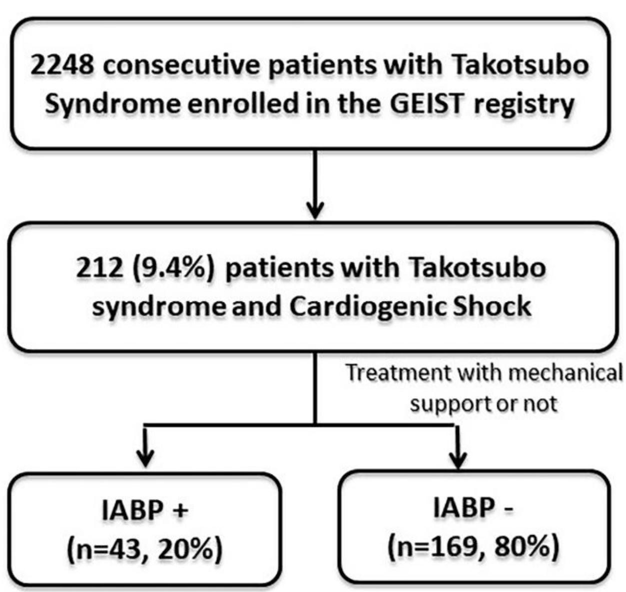


Figure 1 Flow chart of patient's enrolment.

Results

Clinical features of cardiogenic shock in Takotsubo syndrome

CS was observed in 212 (9.4%) of 2248 patients. Mean age of patients with CS was 71 ± 13 years, and one forth (*n* = 53) were male. A stressful trigger was identified in about three-fourths of patients (74%) with similar rate of emotional and physical triggers (38% and 36%, respectively). Admission LVEF was 35 ± 9%, and apical ballooning was the predominant contraction pattern (82%). Mean hospital stay was 16 ± 10 days and in-hospital mortality 16%.

Additional in-hospital complications were as follows: need of invasive ventilation 39% (*n* = 84), need of mechanical cardiac support with intra-aortic balloon pump 20% (*n* = 43), need of inotropic drugs 21% (*n* = 44), ventricular arrhythmias 6% (*n* = 13), stroke 1.8% (*n* = 4), and LV thrombi 1.8% (*n* = 4).

When comparing patients with and without CS. Patients with CS had a higher prevalence of diabetes (27% vs. 19%, *P* < 0.01), previous neurological disorders (21% vs. 14%, *P* < 0.01), male sex (25% vs. 10%, *P* < 0.01), lower LVEF (35 ± 9% vs. 40 ± 12%, *P* < 0.01), and right ventricular involvement (10% vs. 5%, *P* < 0.01) (see Supplementary material online, *Table S1*).

Table 1 Baseline clinical, echocardiographic and laboratory features of patients with Takotsubo syndrome and cardiogenic shock, treated with intra-aortic balloon pump or not

	Cardiogenic shock *n* = 212 Mean	IABP *n* = 43 Mean	No IABP *n* = 169 Mean	*P* value
Age, years	71 ± 13	72 ± 10	70 ± 13	0.41
Male sex	25%	23%	26%	0.41
Hypertension	75%	81%	71%	0.17
Diabetes	27%	29%	23%	0.44
Dyslipidemia	39%	33%	44%	0.20
Smoke	16%	10%	17%	0.25
Neurological disorder	15%	13%	19%	0.33
Emotional stress	38%	23%	39%	0.06
Physical stress	36%	44%	34%	0.23
Hospital stay, days	16 ± 10	16 ± 12	17 ± 9	0.62
Admission LVEF, %	35 ± 9%	36 ± 9%	35 ± 8%	0.72
RV involvement	5%	7%	5%	0.56
LVOTO	7%	2%	8%	0.28
Apical ballooning	82%	86%	90%	0.69
Mid ballooning	16%	14%	8%	0.77
Basal ballooning	2%	0%	2%	0.62
ECG features at admission				
ST elevation	39%	47%	38%	0.30
Long QT	30%	29%	31%	0.79
Negative T waves	50%	49%	51%	0.80

LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction, RV, right ventricular.

Over 212 subjects with Takotsubo syndrome and cardiogenic shock, we had no missing data for age, gender, ballooning type, 3.3–3.7% of missing data for cardiovascular risk factors, 2–12% for comorbidities, 1.4–1.9% for symptoms, 2.4% for LVEF, 10–12% for echo features, 2.3–10–4% for ECG features, and 20% for troponin levels.

Intra-aortic balloon pump use in cardiogenic shock

According to operator choice, 43 patients of 212 (20%) with CS received IABP. No significant differences in terms of age, gender, cardiovascular risk factors, and admission LVEF were found among patients with and without IABP (*Table 1*). Moreover, between two groups, there were no differences in terms of 30-day mortality (16.2% vs. 17%, *P* = 0.98), length of hospitalization (16 ± 12 vs. 17 ± 9, *P* = 0.62), and need of invasive ventilation (35% vs. 41%, *P* = 0.60) (*Table 2*): 30-day survival was not significantly different even at propensity matching analysis (log-rank *P* = 0.735) (*Figure 2*; Supplementary material online, *Table S2*).

Long-term follow-up

At 42-month follow-up, overall-mortality was 35% in patients with CS and TTS and did not differ between patients receiving IABP and not (37% vs. 35%, *P* = 0.72). At multivariate analysis including age, male gender, use of IABP, and LVEF, age and male sex were found as independent predictors of mortality (RR 1.03, 95% CI 1.04–1.06, *P* = 0.01, RR 1.8, 95% CI 1.09–3.2, *P* = 0.02, respectively) (*Table 3*).

Discussion

This study evaluates, in a large multi-centre international registry, the prognostic impact of mechanical support with IABP in patients with TTS and CS (*Graphical Abstract*). We found that the incidence of CS in the present cohort was 9.4%. Mechanical support with IABP did not impact on overall mortality at short and long-term follow-up among TTS patients with CS.

CS is a potential IHC in patients admitted for TTS, with an incidence of 9.4–11.4%.[7,8] Moreover, TTS patients may experience cardiac arrest and need of cardiopulmonary resuscitation with an incidence of 4.9–5%.[24,25] CS in TTS has been associated with higher mortality rates at short- and long-term follow-up; therefore, an optimal management is crucial.[6,7,26]

In this setting, support with inotropes should be avoided given their potential role in pathogenesis of TTS. Catecholamines could induce depression of cardiomyocytes mainly on β2 adrenergic receptors that can be mainly found on apical LV segments.[27] Indeed, in a study by Ansari

Table 2 In-hospital complications in patients with cardiogenic shock treated with intra-aortic balloon pumping and not

	IABP (*n* = 43)	NO IABP (*n* = 169)	*P* value
Invasive ventilation during hospitalization	35% (*n* = 15)	41% (*n* = 69)	0.60
Stroke	4% (*n* = 2)	1% (*n* = 2)	0.13
Left ventricular thrombus	2% (*n* = 1)	2% (*n* = 3)	0.81
Ventricular arrhythmias	4.6%(*n* = 2)	6.5% (*n* = 11)	0.88
Catecholamine infusion	11% (*n* = 5)	23% (*n* = 39)	0.14
In-hospital death	11% (*n* = 5)	17% (*n* = 29)	0.14
Length of hospitalization (mean days)	16 ± 12	17 ± 9	0.62

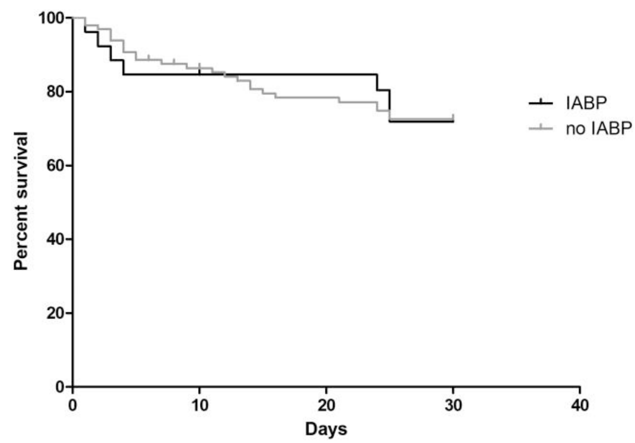


Figure 2 Kaplan–Meier curves with overall survival in patients treated with intra-aortic balloon pump at 30-day follow-up and not. No differences were found between patients receiving intra-aortic balloon pump and not (log-rank $P = 0.73$).

Table 3 Multivariable analysis of independent predictors of mortality at long-term among Takotsubo syndrome patients

	Multivariable analysis RR (95% CI)	*P* value
Age, years	1.03 (1.01–1.06)	0.01
Male sex	1.88 (1.09–3.24)	0.02
Intra-aortic balloon pump	0.75 (0.43–1.33)	0.33
Admission LVEF, %	4.79 (0.28–80.916)	0.27

LVEF, left ventricular ejection fraction.

et al.[12] comparing TTS patients treated with and without catecholamine support, 30-day mortality (51.4% vs. 17.2%, $P < 0.01$) as long-term mortality (80.9% vs. 38.7%, $P < 0.01$) was significantly higher in the first group. Other pharmacological options are the use of intravenous levosimendan[11] or short-acting β1 selective blockers (esmolol)[13] in case of LV outflow tract obstruction.

Mechanical circulatory support could represent an option in patients with TTS and CS and can be used as a bridge-to-recovery strategy. TTS haemodynamics are featured by severely increased filling pressures in the absence of shock, probably due to stunning-related impairment of myocardial compliance and relaxation. Currently, there are three different percutaneous support systems mainly used: IABP, extracorporeal membrane oxygenation (ECMO), and microaxial pumps (i.e. Impella™, Abiomed).

IABP reduces afterload in systole, increasing coronary blood flow during diastole. IABP could be harmful in patients with TTS, as deflation of the IABP during systole may increase the transaortic gradient[28] and thereby induce or aggravate LV outflow tract obstruction.[29] If used, it is mandatory to evaluate LV outflow tract before IABP implantation through echocardiogram. Few data have been published on IABP and TTS, and only some case report evaluated the use of IABP in TTS with CS[30,31] and after resuscitation.[32]

Veno-arterial ECMO drains blood from the right atrium and provides oxygenated blood to the lower tract of the abdominal aorta.[33] ECMO is a potential therapeutic strategy during right ventricular failure; the procedure inducing right-to-left shunt reduces preload and increases organ perfusion enhancing afterload. However, this may have some several side effects as worsening mitral regurgitation and pulmonary oedema during outflow tract obstruction. According to the current literature, ECMO has been used in patients with TTS and CS[34] or in refractory arrest.[35]

Micro-axial pumps as Impella drain blood from the LV and expel it to the aorta, providing antegrade blood flow. It drains blood during systole and diastole unloading the LV and contributes to myocardial recovery. Impella bridges LV outflow tract obstruction and is a therapeutic option for those cases where CS is complicated by LV outflow obstruction.[36] Currently, only a case series of 16 patients evaluated the safety and efficacy of Impella with potential benefit in term of in-hospital mortality.[37]

Although in several case report the use of mechanical support in TTS appears to be safe as a bridge to myocardial recovery, there are no data on long-term outcome. The present study reports the impact of IABP on survival in TTS patients with CS. According to the present study, IABP has no impact on mortality at short- and long-term follow-up. In the present study, in-hospital mortality was not affected in patients treated or not with IABP (11% vs. 17%, $P = 0.14$). This trend was also observed at 30-day follow-up, with similar mortality between patient treated with IABP and not (16.2% vs. 17%, $P = 0.98$).

These data reflect previous randomized studies that evaluated mechanical support in myocardial infarction and CS. Thiele *et al.*[38] found in a randomized open-label trial that IABP has no impact on survival among patients with CS and myocardial infarction at short- and long-term.

Moreover, recently Miller *et al.*[39] in a propensity-matched analysis of patients with acute myocardial infarction complicated by CS found that mechanical circulatory support with IMPELLA was associated with increased short-term and 1-year risk of mortality, bleeding, and cost compared with IABP. Therefore, the use of mechanical support in the context of CS is still debated, and a tailored approach is needed.

According to our data, IABP cannot be generally recommended in TTS patients with CS. The main reason for the missing effect of IABP on mortality in TTS might be the fact that mortality in TTS is mainly driven by non-cardiovascular comorbidities.[40,41] Randomized trials are needed in this context to evaluate the best pharmacological treatment to improve survival in TTS patients with CS.

Limitations

The German Italian Spanish Takotsubo registry is a multi-centre observational registry in which data were collected from several different institutions. This is not a randomized trial, and use of IABP was left at operator choice. Although data were prospectively collected, analysis was performed retrospectively. The study has no control group for patients with CS. Due to the small sample size of patients with TTS and CS, even after several statistical analysis as logistic regression and propensity score matching, a residual bias cannot be completely excluded. The final sample of patients with CS may be not powered enough to detect a significant difference in terms of mortality. Kind of vasopressor and dosages were not prospectively recorded. Troponin and BNP values were collected with different unit of measures and therefore were not reported in the present study. Weaning from mechanical circulatory support was performed when systolic blood pressure was higher than 90 mmHg for >30 min; however, a multiparametric approach could be considered.[42]

Conclusions

In a large multi-centre observational registry, the use of IABP was not associated with lower mortality rates at short- and long-term follow-up in patients with TTS and CS.

Lead author biography

Francesco Santoro, MD, PhD, is cardiologist at the University hospital of Foggia, Policlinico Riuniti, Italy. In 2013, he completed his training at Texas Arrhythmia Institute, Austin, TX, USA, under the supervision of Dr. Andrea Natale, and, in 2015–18, at electrophysiology laboratory at the Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany. His research fields include: Cardiomyopathies (Takotsubo syndrome) and catheter ablation of atrial fibrillation and ventricular tachycardia. He authored 180 publications in indexed journals, about 175 abstracts and 6 electrophysiology book chapters.

Data availability

Data would be available on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: None declared.

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