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ORIGINAL RESEARCH ARTICLE

Incidence and clinical/laboratory correlates of early hypotension in takotsubo syndrome

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Abstract

Aims Takotsubo syndrome (TTS) is a form of acute myocardial inflammation, often triggered by catecholamine release surges, which accounts for approximately 10% of 'myocardial infarctions' in female patients above the age of 50. Its associated substantial risk of in-hospital mortality is mainly driven by the development of hypotension and shock. While hypotension is induced largely by factors other than low cardiac output, its precise cause is unknown, and clinical parameters associated with hypotension have not been identified previously. We therefore sought to identify the incidence and clinical/laboratory correlates of early hypotension in TTS.

Methods and results We analysed the in-hospital data of patients recruited to the South Australian TTS Registry. Associations between the development of hypotension, patient demographics, severity of the acute TTS attack, and key biochemical markers were sought. One hundred thirteen out of 319 patients (35%) were hypotensive (median systolic blood pressure 80 mmHg) during their index hospitalization. Development of hypotension preceded all in-hospital deaths (n = 8). On univariate analyses, patients who developed hypotension had lower left ventricular ejection fraction (P = 0.009), and higher plasma N-terminal pro brain natriuretic peptide and troponin-T concentrations (P = 0.046 and 0.008, respectively), all markers of severity of the TTS attack; hypotension also occurred less commonly in male than in female patients (P = 0.014). On multivariate linear regression analysis, female sex and lower left ventricular ejection fraction were independent correlates of the development of hypotension (P = 0.009 and 0.010, respectively).

Conclusions Early development of hypotension is very common in TTS, and its presence is associated with a substantial risk of in-hospital mortality. Hypotension is a marker of severe TTS attacks and occurs more commonly in female TTS patients.

Keywords Takotsubo syndrome; Hypotension; Left ventricular dysfunction; NT-proBNP

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Introduction

Takotsubo syndrome (TTS) is an acute inflammatory cardiac condition, often precipitated by 'pulse' exposure to catecholamines. For the first few years after it was originally described by Japanese investigators in 1990,[1] TTS was thought to be rare and benign. However, it is now generally recognized that TTS is not only common, accounting for up to 10% of suspected acute S-T segment elevation acute myocardial infarction presentations in aging female patients,[2] but also associated with substantial morbidity and mortality.[3]

Complications of TTS can occur both early and late. In the early stages, there is a risk of hypotension and shock,[4] tachyarrhythmias,[5] heart block,[6] and the development of mural left ventricular (LV) thrombus.[7] There are also reports of LV rupture.[8] In the longer term, patients often experience persistent impairment of quality of life.[9] There is also a substantial risk of late recurrence, occurring in 2–3% of patients per annum.[10] The long-term mortality rate following TTS episodes is similar to that after acute coronary syndromes.[11]

By far the most common and most life-threatening in-hospital complication is the development of hypotension and shock. Surprisingly, the exact cause of early hypotension in TTS is not completely understood, with our previous studies finding no significant correlation between systolic blood pressure and either extent of LV systolic dysfunction or

diminution in cardiac output.[12] In the absence of mechanistic understanding, the management of shock in TTS is also challenging, as catecholamine administration is both harmful and likely to be ineffective on theoretical grounds.[13] Early hypotension not only represents a common cause of in-hospital mortality but has also been implicated as a predictor of late mortality risk.[14]

In the current study, we utilized a large and detailed database of TTS patients to identify both the incidence of early hypotension/shock and clinical/laboratory parameters which correlate with the risk of this complication in individual patients.

Methods

This study protocol conforms to the ethical guidelines of the Declaration of Helsinki (Br Med J 1964; ii: 177) and is approved by the local Human Research Ethics Committee. Data from consecutive patients admitted with TTS to three tertiary hospitals in Adelaide, Australia, were analysed. Patients had provided informed consent to participate in the South Australian (SA) TTS registry. Diagnosis of TTS was made on the basis of Mayo Clinic criteria,[15] supplemented wherever practicable by performance of cardiac magnetic resonance imaging within 5 days of admission.[16] Baseline patient data, including age, sex, comorbidities and prior therapy, were documented, as were in-hospital clinical data, including lowest recorded systolic blood pressures. Hypotension was defined as a systolic blood pressure of $\leq$90 mmHg. Patients who developed TTS in relation to a potentially life-threatening physical illness were classified as 'secondary' TTS,[17] while the remainder of the patients were classified as 'primary' TTS.

Patients' venous blood samples were collected in the acute setting. Plasma concentrations of normetanephrine were measured at the time of diagnosis. N-terminal pro brain natriuretic peptide (NT-proBNP), C-reactive protein, and troponin-T were measured serially, and peak concentrations during the hospital stay were recorded.

Transthoracic echocardiography was also performed during the acute presentation. Standard apical two-chamber, three-chamber, and four-chamber views were obtained with special attention to LV endocardial definition. LV ejection fraction (LVEF) was then calculated using the Simpson's biplane method.

For univariate comparison of patients who developed hypotension with those who did not, we used unpaired *t* tests/Wilcoxon tests or χ^2 tests/Fisher's exact test as appropriate. This was followed by a backwards stepwise multivariate linear regression analysis, forcing into this analysis the parameters indicated in *Table 1*, irrespective of the results of univariate comparisons. Potential status of mutually correlated parameters as confounders on multivariate analyses was evaluated utilizing Pearson's or Spearman's correlation coefficient as appropriate. This methodology was designed to facilitate evaluation of potential correlates of hypotension according to differences in patient demographics, type of TTS, associated disease states, admission treatments, and markers of TTS attack severity. The limit of statistical significance was set at $P < 0.05$. Data are presented as mean ± SD or median (interquartile range) as appropriate.

Table 1 Parameters included in multivariate analysis as potential correlates of development of hypotension

Parameters included in the multivariate analysis	
Patient demographics	Age
	Sex
Clinical characteristics	Primary/secondary TTS
	Apical/non-apical hypokinesis
Comorbidities	Hypertension
	Diabetes mellitus
Admission medications	ACE inhibitors/ARBs
Laboratory parameters	Estimated GFR
	Plasma NT-proBNP, troponin-T, CRP, and normetanephrine concentrations
Echocardiographic parameters	Acute LVEF

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRP, C-reactive protein; GFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide; TTS, takotsubo syndrome.

Results

Data from 319 TTS patients were analysed. Patients' demographics and baseline characteristics are summarized in *Table 2*. A total of 113 (35%) patients were hypotensive early during hospitalization. Of those patients, 20 (17%) required admission to intensive care units, where all received infusions of positive inotropic agents. Hypotension occurred more frequently among female than male patients and tended to be less frequent among patients with histories of hypertension. On the other hand, prior treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was not associated with any increase in frequency of hypotension.

Table 3 shows the clinical, biochemical, and echocardiographic differences between patients who developed hypotension and those who did not. A total of 8 (2.5%) patients died in hospital: all of these had developed hypotension during acute presentation ($P < 0.001$, Fisher's exact test). LV outflow tract (LVOT) obstruction (peak $\geq$30 mmHg LVOT gradient) was present in only 6 (2%) patients, but was significantly associated with hypotension ($P = 0.019$).

The extent of anomalies of all the parameters tested, whether indicative of haemodynamic disturbance or of inflammatory activation, tended to be greater in patients who developed hypotension. Of these, the significantly different

Table 2 Patient demographics and baseline characteristics: comparison of patients who developed vs. those who did not develop hypotension

	Total (n = 319)	Hypotensive (n = 113)	Not hypotensive (n = 206)	P value
Age [years; median (IQR)]	68 (60–77)	67 (60–77)	69 (60–78)	0.303
Male (n; %)	24 (8%)	3 (3%)	21 (10%)	0.014
Secondary TTS (n; %)	81[a] (25%)	33[a] (29%)	48 (23%)	0.237
Apical TTS (n; %)	209 (65%)	74 (65%)	135 (65%)	0.983
Diabetes mellitus (n; %)	51 (17%)	19 (18%)	32 (16%)	0.577
Hypertension (n; %)	158 (51%)	46 (44%)	112 (55%)	0.069
Prior use of ACE inhibitors/ARB (n; %)	125 (42%)	37 (36%)	88 (45%)	0.128

Significance values relate to comparisons of normotensive and hypotensive patients.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range; TTS, takotsubo syndrome.
[a]A total of 14 of patients with secondary TTS had underlying sepsis. Seven of them developed hypotension.

Table 3 Clinical and laboratory differences between hypotensive vs. not hypotensive patients

	Hypotensive (n = 113)	Not hypotensive (n = 206)	P value
Lowest systolic blood pressure [mmHg; median (IQR)]	80 (78–86)	105 (100–110)	<0.001
In-hospital mortality (n; %)	8 (7%)	0 (0%)	<0.001
Estimated GFR [mL/min; median (IQR)]	60 (57–80)	62 (60–86)	0.035
LVEF [%; mean ± SD]	44 ± 11	48 ± 11	0.009
LVOT obstruction[a] (n; %)	5 (4%)	1 (0.5%)	0.019
NT-proBNP [ng/L; median (IQR)]	4714 (2781–11109)	4120 (2410–7186)	0.046
Troponin-T [ng/L; median (IQR)]	480 (261–775)	368 (200–599)	0.008
CRP [mg/L; median (IQR)]	13 (4–54)	10 (5–31)	0.296
Plasma metanephrine [pmol/L; median (IQR)]	1060 (680–1570)	970 (650–1380)	0.491

CRP, C-reactive protein; GFR, estimated glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro brain natriuretic peptide.
[a]LVOT obstruction (peak LVOT gradient ≥30 mmHg on echocardiography).

parameters were lower estimated glomerular filtration rates and LVEF, and higher plasma NT-proBNP and troponin-T concentrations in the hypotensive group. *Figure 1* illustrates the distribution of data for LVEF, peak NT-proBNP, and troponin-T concentrations.

On multivariate linear regression analysis, female sex and lower LVEF were found to be independent correlates of the development of hypotension (β = −0.22, P = 0.009 and β = −0.21, P = 0.010, respectively).

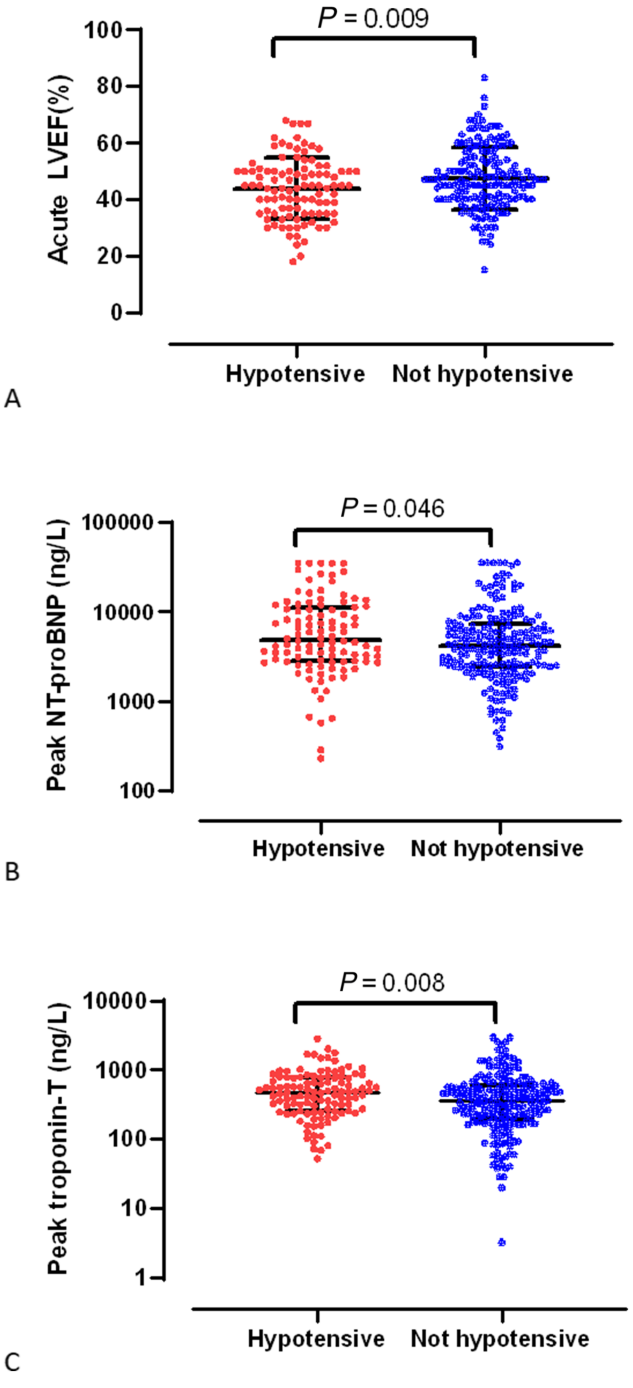
Discussion

The occurrence of hypotension and shock in the acute stages of TTS represents one of the most common and feared early complications of the disorder. Previous registry publications, including one emanating from the InterTAK group (and thus utilizing overlapping data from the current study), recently showed that the development of shock is associated with a substantial risk of both in-hospital and long-term mortality.[14] The current data confirm that hypotension per se, with or without clear-cut shock, represents a substantial risk factor for short-term mortality. Intriguingly, hypotension was also associated with data suggesting more severe attacks of TTS (*Table 3*). Consistent with the previous publication from the InterTAK group,[14] we also found that acute LVEF was statistically lower in patients with hypotension both on univariate and multivariate analyses. Other parameters of severity of TTS attacks, including plasma NT-proBNP and troponin-T concentrations, however, were not statistically significant correlates of hypotension on multivariate analysis. We also found that acute LVEF correlates closely and inversely with plasma NT-proBNP and troponin-T concentrations (*Figure 2*). Therefore, the presence of low LVEF is predictive of greater elevation of NT-proBNP and troponin-T concentrations and acts partially as a 'confounder' on multivariate analysis. Conversely, peak plasma NT-proBNP concentrations of >10 000 ng/L were associated with increased probability of early hypotension (51% vs. 32%; P = 0.006). The other major findings from the current study are that hypotension is more likely to occur (both on a univariate and multivariate basis) in female patients, with no obvious association with 'secondary' TTS (a disorder more commonly affecting male patients).

As regards the potential mechanistic implications of the current findings, there are, unfortunately, many residual unanswered questions. The first of these is the precise *cause* of the hypotension. In this regard, results of two recent investigations are relevant. We have published that

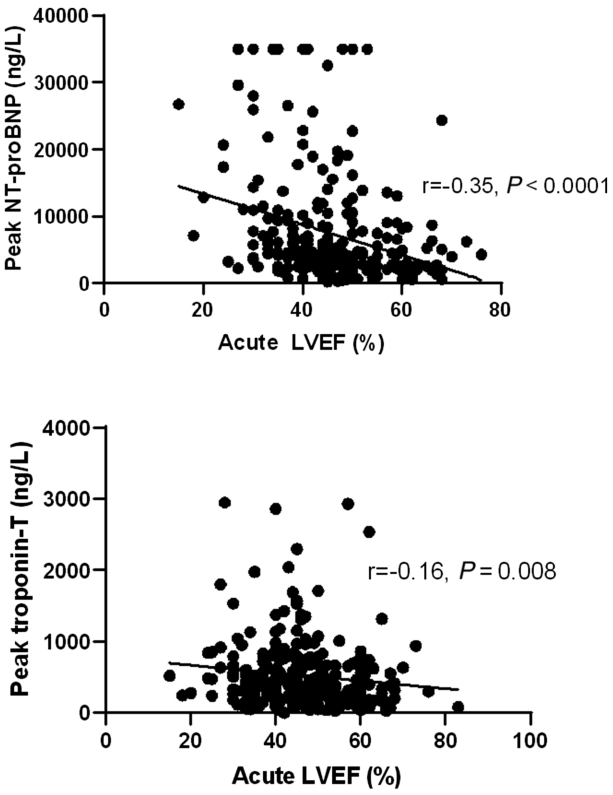
a. hypotension is neither associated with substantial increases in right heart pressures nor decreases in

Figure 1 Univariate analyses of the association between the development of hypotension and severity of acute takotsubo syndrome attacks [(A) acute left ventricular ejection fraction (LVEF), (B) peak N-terminal pro brain natriuretic peptide (NT-proBNP) concentrations, and (C) peak troponin-T concentrations]. All comparisons were made by non-paired t-tests, and *p*-values are indicated on the figure.



(implied) cardiac output values,[12] raising the issue that the problem may relate to *inappropriate peripheral vasodilatation*.

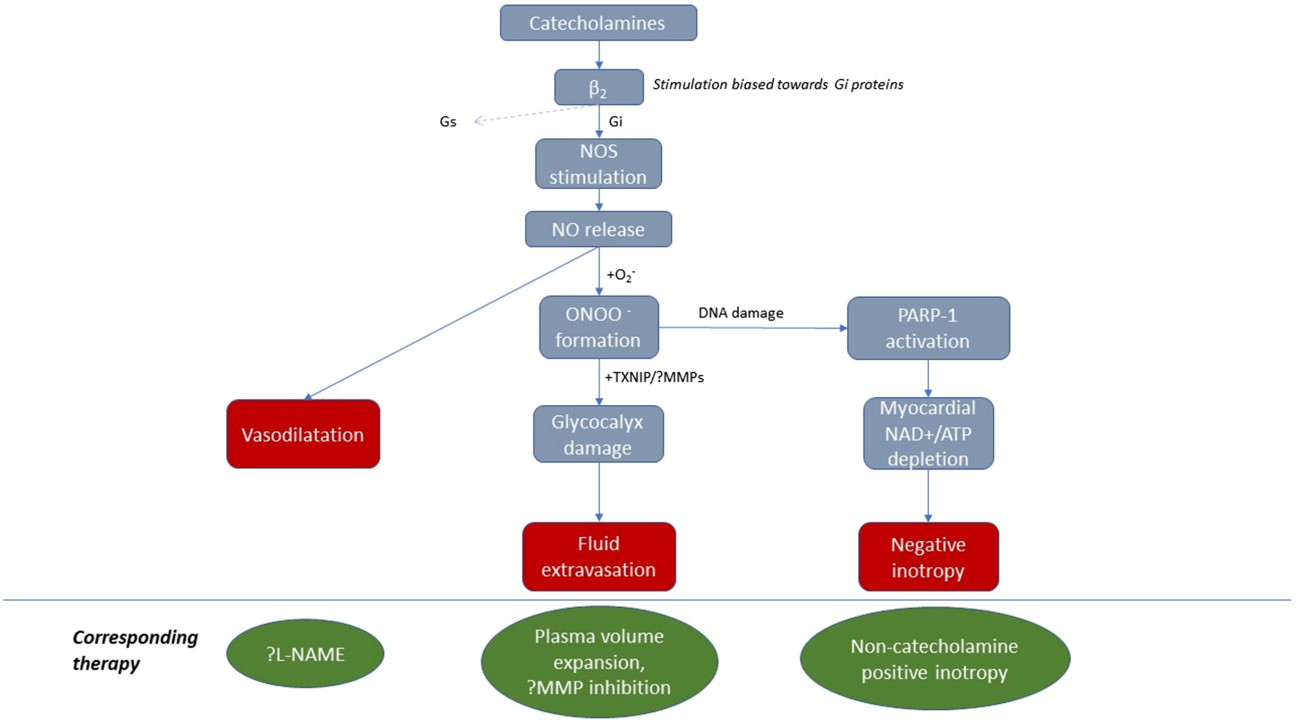
Figure 2 Evaluation of potential for 'confounder' status between parameters of severity of takotsubo syndrome attack [(A) correlation between acute left ventricular ejection fraction (LVEF) and peak N-terminal pro brain natriuretic peptide (NT-proBNP) concentrations, and (B) correlation between acute LVEF and peak troponin-T concentrations]. Data were analysed using Spearman's correlation coefficient, and significance levels are shown. Note that the upper limit of quantitation for the assay utilized to measure plasma concentrations of NT-proBNP was 35 000 ng/L.



b. hypotension is not engendered by right ventricular involvement in TTS[18] and is therefore not analogous with hypotension complicating right ventricular infarction.

Interestingly, we have also demonstrated that TTS is associated with paradoxically low plasma concentrations of the endogenous nitric oxide (NO) synthase inhibitor asymmetric dimethyl arginine and with hyper-reactivity of platelets to the anti-aggregatory effects of NO donors[19]: in combination, these findings suggest that TTS may be associated with *increases in both NO generation and effect*. Furthermore, during the early stages of TTS, there is variable release into the circulation of the endothelial glycocalyx component syndecan-1, indicating inflammatory damage to the endothelium, with resultant *increase in vascular permeability*.[20] Thus, it is possible that both excessive NO-mediated dilatation and depletion of intravascular volume may contribute to the development of hypotension. These novel pathogenetic concepts related to mechanisms underlying the development of hypotension are synthesized in *Figure 3*.

Figure 3 Early hypotension/shock in takotsubo syndrome: postulated inotropic vs. non-inotropic components of pathogenesis. Abbreviations: β2, β2 adrenoceptors; ATP, adenosine triphosphate; Gi, G-inhibitory; Gs, G-stimulatory; L-NAME, L-NG-nitro-arginine methyl ester (NOS inhibitor); MMPs, matrix metalloproteinases; NAD^+, nicotinamide adenine dinucleotide; NO, nitric oxide; NOS, nitric oxide synthase; O_2^-, superoxide; $ONOO^-$, peroxynitrite; PARP-1, poly [ADP-ribose] polymerase 1; TXNIP, thioredoxin interacting protein.



These findings argue for the use of fluid replacement as the primary therapeutic option in TTS, as opposed to the more commonly used treatment of infusion of catecholamines (a theoretically undesirable idea) and other pressor agents.

It remains far from certain why hypotension, as shown from the current analysis of a large data set, reflects not only low LVEF but also other markers of a 'large attack'. The first possibility is that hypotension simply reflects substantial impairment of LV contractility and that the resultant falls in low cardiac output is the main precipitant of hypotension. This seems unlikely, especially as a sole precipitant, given the apparent preservation of cardiac output.[12] The second possibility is that both poor LV systolic function and essentially vasodilator hypotension are products of the same stimuli and tend to be proportionate without significant direct interaction, potentially exacerbated by impaired reflex tachycardic responses. In theory, end-organ refractoriness to the positive inotropic and vasoconstrictor effects of catecholamines[21] might contribute to such a 'balanced' concordance. The third, and theoretically perhaps the most attractive possibility, is that the extent of glycocalyx shedding might represent the common pathogenetic factor, causing hypotension via fluid 'leakage' and myocardial inflammation via permeabilization to monocyte and neutrophil ingress and subsequent intracardiac inflammation.[22,23] Furthermore, pleural and pericardial effusions are commonly found in TTS[24,25] and may appear independent of the impairment in cardiac output. This idea could in theory be progressed by studying the effects of inhibitors of glycocalyx shedding, such as the non-specific matrix metalloproteinase inhibitor doxycycline.[26]

In the absence of identification of clinical correlates of TTS-associated hypotension, which clearly identify its causes, there can be no single 'message' regarding either prevention or treatment of the problem. However, if we are to assume that early hypotension results both from impaired contractility (reduced stroke volume) and systemic circulatory (inappropriate vasodilatation and increases in vascular permeability) anomalies, a therapeutic approach addressing the full spectrum of these pathogenetic factors (as shown in *Figure 3*) seems appropriate.

While the implications of early hypotension on long-term survival were not explored in this study, it must be noted that hypotension has both short-term and long-term adverse prognostic implications.[14] We also did not explore the implications of variations in early modes of treatment in TTS, but none of the hypotensive patients were treated with plasma volume expansion. A further limitation is that we did not fully explore the implications of the presence/absence of LVOT

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obstruction,[27] other than confirming its univariate association with hypotension and its relative rarity. Nevertheless, these results leave unanswered the issue of whether LVOT obstruction contributes directly to the development of hypotension, or indirectly as a component of larger TTS attacks. Finally, we elected to adopt a qualitative, rather than quantitative, approach to hypotension, because the majority of patients who developed severe hypotension were eventually treated with pressor agents.

Conclusion and potential implications

The results of the current study show that early hypotension/shock occurs in approximately one third of TTS cases and represents a strong predictor of in-hospital death. Hypotension appears to reflect evolution of more severe attacks of TTS and not to result purely from reductions in LV contractility.

It needs to be recognized clinically that the acute phase of TTS is associated not only with regional impaired LV contractility (and occasionally with LVOT obstruction), but also with important but transient extracardiac anomalies. These potentially reduce peripheral vascular resistance[19] and also cause fluid extravasation into the extravascular space[20] (accounting for development of pleural and pericardial effusions). However, to date, none of the clinical strategies utilized for management of hypotension/shock have taken this into account. Development via controlled clinical trials of effective methods for simultaneously limiting hypotension and size of TTS attacks remains a major medical priority.

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