International Journal of Cardiology 333 (2021) 45–50

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Indications of beta-adrenoceptor blockers in Takotsubo syndrome and theoretical reasons to prefer agents with vasodilating activity

Alberto Aimo [a,b,*], Francesco Pelliccia [c], Giorgia Panichella [a], Giuseppe Vergaro [a,b], Andrea Barison [a,b], Claudio Passino [a,b], Michele Emdin [a,b], Paolo G. Camici [d]

[a] *Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy*
[b] *Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy*
[c] *Department of Cardiovascular Sciences, Sapienza University, Rome, Italy*
[d] *San Raffaele Hospital and Vita Salute University, Milan, Italy*

ARTICLE INFO

Article history:
Received 23 February 2021
Accepted 25 February 2021
Available online 2 March 2021

Keywords:
Myocardial infarction
Takotsubo syndrome
Sympathetic activation
β-Blockers

ABSTRACT

Takotsubo syndrome (TTS) is estimated to account for 1–3% of all patients presenting with suspected ST-segment elevation myocardial infarction. A sudden surge in sympathetic nervous system is considered the cause of TTS. Nonetheless, no specific recommendations have been provided regarding β-blocking therapy. Apart from specific contra-indications (severe LV dysfunction, hypotension, bradycardia and corrected QT interval >500 ms), treatment with a β-blocker seems reasonable until full recovery of LV ejection fraction, though evidence is limited to a few animal studies, case reports or observational studies. In this review, we will reappraise the rationale for β-blocker therapy in TTS and speculate on the pathophysiologic basis for preferring non-selective agents with vasodilating activity over β_1-selective drugs.

Takotsubo syndrome (TTS) is characterized by transient left ventricular (LV) systolic dysfunction triggered by physical or emotional factors with clinical features resembling those of an acute coronary syndrome [1–3]. Its typical presentation consists in a dilation and dysfunction of apical LV segments (apical ballooning) with preserved or increased contractility of basal segments that may lead to LV outflow tract obstruction (LVOTO) in about 20% of cases [4] (Table 1). No specific medical treatment has been demonstrated to protect against in-hospital mortality and promote the short-term recovery from LV dysfunction [5]. Equally, there is no medication able to prevent recurrences. Retrospective registry data have shown that angiotensin converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs), but not β-blockers, are associated with improved survival at one-year follow-up in patients with or without heart failure (HF) [3]. However, randomized clinical trials with pre-specified end-points are lacking, and therefore no definitive data on the safety and efficacy of agents are available. In this review, we will focus on the rationale and possible applications of β-blockers in patients with TTS, and the theoretical reasons to prefer β-blockers with a vasodilating activity due to concomitant α_1 adrenoceptor blockade.

* Corresponding author at: Institute of Life Sciences, Scuola Superiore Sant'Anna, and Cardiology Division, Fondazione Toscana Gabriele Monasterio, Piazza Martiri della Libertà 33, 56124 Pisa, Italy.
E-mail addresses: a.aimo@santannapisa.it, aimoalb@ftgm.it (A. Aimo).

1. Current recommendations about β-blockers in TTS

During the acute phase, β-blockers should be considered in patients with mild forms of TTS, either with or without HF, and in those with HF or pulmonary edema. Furthermore, patients with hypotension or cardiogenic shock and evidence of LVOTO might benefit from the infusion of short-acting β-blockers, which might rapidly relieve LVOTO. β-blockers might also be considered in patients with arrhythmias (for example, ventricular tachycardia or fibrillation), but should be avoided when patients are bradycardic and have a corrected QT interval >500 ms. Finally, β-blockers have not been recommended for chronic treatment after discharge (Fig. 1). These suggestions for patient management are reported in an international consensus document and rely on expert opinion, in the absence of specific evidence [5]. (See Fig. 2.)

2. Evidence on β-blockers in TTS

Data about β-blocker therapy during the acute phase of TTS are limited to a few animal studies showing that the apical ballooning is attenuated after the administration of metoprolol (a selective β_1-blocker) [6], or amosulalol (a drug with a much higher affinity for α_1-adrenoceptors than for β-receptors) [7], and to some case reports or observational studies [8–11] (Table 2).

After the acute phase, long-term β-blocker therapy has been proposed to prevent TTS recurrence or attenuate its clinical severity by

https://doi.org/10.1016/j.ijcard.2021.02.074
0167-5273/

Table 1
The International Takotsubo (InterTAK) diagnostic criteria.

1. Patients show transient[a] LV dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. RV involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS)[b].
2. An emotional, physical, or combined trigger can precede the TTS event, but this is not obligatory.
3. Neurologic disorders (e.g., subarachnoid hemorrhage, stroke/TIA, or seizures) as well as pheochromocytoma may serve as triggers for TTS.
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of BNP is common.
6. Significant CAD is not a contradiction in TTS.
7. Patients have no evidence of infectious myocarditis[b].
8. Postmenopausal women are predominantly affected.

[a] Regional wall motion abnormalities may remain for a prolonged period of time or documentation of recovery may not be possible. For example, death before evidence of recovery is captured.
[b] Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of TTS. BNP, B-type natriuretic peptide; CAD, coronary artery disease; ECG, electrocardiogram; LV, left ventricular; RV, right ventricular; TIA, transient ischemic attack; TTS, Takotsubo syndrome. Adapted from: Ghadri et al., 2018 [5].

blunting the effects of further catecholamine surges. However, no study has proven any clear benefit of long-term treatment with β-blockers so far. In a registry of 1750 patients, Templin et al. showed comparable death rates at 1 year whether patients with TTS are treated with β-blockers or not [3]. In an observational study of 2672 patients, β-blockers were unable to lower 30-day mortality [10]. A meta-analysis by Singh et al. concluded that β-blockers do not prevent TTS recurrence, contrary to ACE inhibitors [12]. Similarly, the meta-analysis by Bonacchi et al. including 8 studies and 511 patients found no difference in terms of recurrence rate between patients receiving β-blockers and those who were not [13], and the meta-analysis by Santoro showed that TTS severity is not affected by pre-treatment with low-dose β-blockers [14].

In summary, available data on β-blockers in both the acute and sub-acute phases of TTS have yielded unclear results. A potential explanation of the controversial findings reported so far may lie on the fact that the optimal use of β-blockers in TTS requires understanding of the complex pathophysiologic mechanisms underlying this condition.

2.1. Pathophysiology of TTS and role of sympathetic activation

The sympathetic nervous system regulates both inotropic and chronotropic cardiac functions as well as vasomotion directly, through norepinephrine released from its myocardial nerve endings, and indirectly, through circulating catecholamines released from the adrenal gland. In addition, increased catecholamine levels promote positive

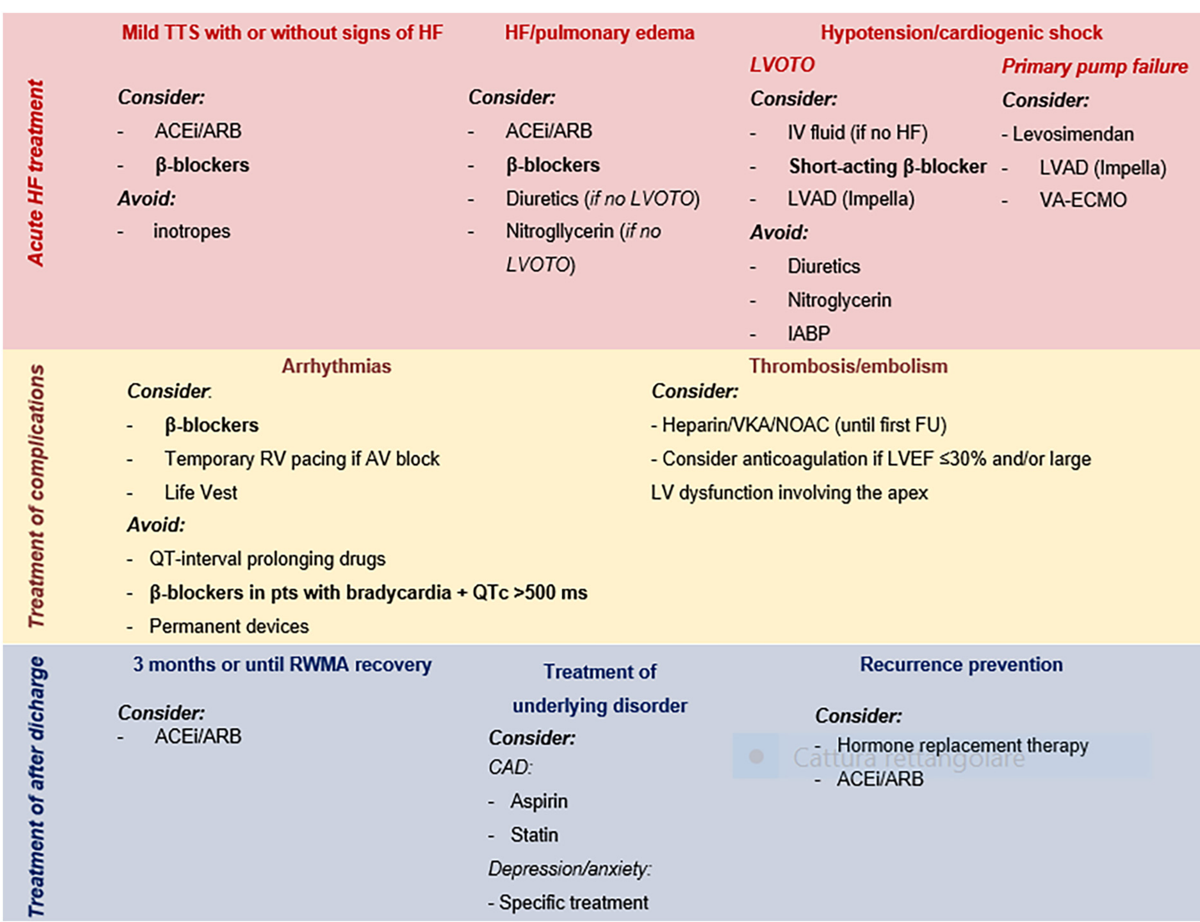

Fig. 1. Recommendations on the management of Takotsubo syndrome (TTS). ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AV, atrioventricular; CAD, coronary artery disease; FU, follow-up; HF, heart failure; IABP, intra-aortic balloon pump; IV, intravenous; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; NOAC, non-vitamin K antagonist; QTc, corrected QT interval; RV, right ventricular; RWMA, regional wall motion abnormality; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VKA, vitamin K antagonist. Modified with permission from: Ghadri JR et al., 2018 [5].

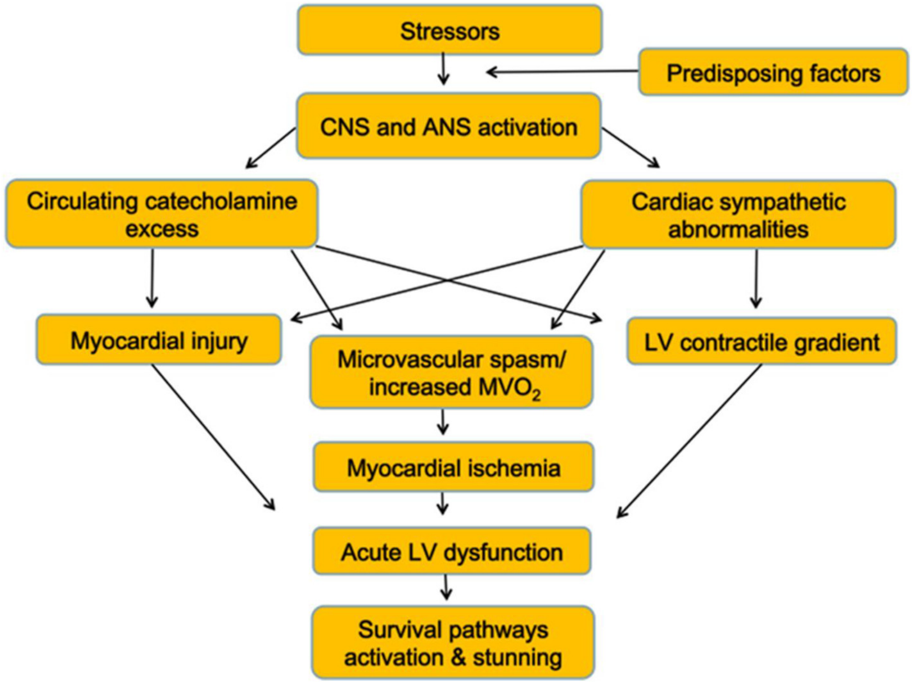

Fig. 2. Key pathogenetic elements in Takotsubo syndrome. The interplay among triggers, pathogenetic factors, mechanisms of cardiac injury, and clinical consequences is reported. ANS, autonomic nervous system; CNS, central nervous system; LV, left ventricular; MVo_2, myocardial oxygen consumption. Reprinted with permission from: Pelliccia F et al., 2017 [24].

Table 2
Studies assessing the effects of β-blocker therapy during the acute phase of Takotsubo syndrome (TTS).

Study	Type of study	Drug	Receptors targeted	Main results
Ueyama et al., 2002 [7]	Preclinical (rats with emotion-induced TTS)	Amosulalol	α_1 β_1 β_2	LV apical ballooning prevented by pre-treatment with amosulalol.
Izumi et al., 2009 [6]	Preclinical (monkey with epinephrine-induced TTS)	Metoprolol	β_1	Earlier LVEF recovery and diminished cardiomyocytolysis.
Kumar et al., 2011 [11]	Clinical (collection of case reports on patients with TTS)	Several β-blockers	–	β-blocker therapy may have protective effect against cardiac rupture.
Santoro et al., 2016 [9]	Clinical (retrospective observational study, patients with TTS and LVOTO)	Esmolol	β_1	Esmolol infusion temporally associated with reduction in intraventricular gradient and systemic blood pressure.
Isogai et al., 2016 [10]	Clinical (retrospective observational study, patients with TTS)	Several β-blockers: propranolol, landiolol, esmolol, carvedilol, bisoprolol, others	β_1 β_2 (propranolol) β_1 (landiolol, esmolol, bisoprolol) α_1 β_1 β_2 (carvedilol)	No significant association between early β-blocker use and in-hospital mortality.

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

lusitropy, enabling the heart to relax more rapidly. This effect is mediated by the phosphorylation of phospholamban and troponin I via a cyclic adenosine monophosphate-dependent pathway. Catecholamine-induced calcium influx into the sarcoplasmic reticulum increases both inotropy and lusitropy [15].

Considerable evidence exists of an association between a sudden surge in sympathetic activity and TTS. This includes: a) the frequency of emotional or physical triggers, b) the possibility to experimentally induce TTS by intravenous infusion of catecholamines and β-agonists, c) the evidence of adrenergic activation from measurement of circulating catecholamines, heart rate variability studies, microneurography, and myocardial scintigraphy with ^{123}I-meta-iodobenzylguanidine [2], and d) the histopathologic finding of contraction band necrosis typical of direct catecholaminergic toxicity [16]. A cause-effect relationship is thought to exist between sympathetic activation and TTS.

The paroxysmal sympathetic activation may lead to LV dysfunction through multiple mechanisms, including 1) a spasm of small arteries and arterioles causing myocardial ischemia followed by stunning, 2) direct toxic effects of catecholamines on cardiomyocytes, and 3) the activation of cellular survival pathways that may contribute to the transient impairment of LV contraction (Fig. 1). These mechanisms are not mutually exclusive and their relative importance may vary in each individual patient.

2.2. Spasm of small arteries and arterioles

Both α- and β-adrenoceptors are present in the coronary vasculature, but with different distributions. The large epicardial coronary arteries have a conduit function and offer little resistance to coronary blood flow. Small arteries have diameters ranging from 100 to 500 μm, are characterized by a measurable pressure drop along their length, are not controlled by myocardial metabolites, and express α_1-adrenoceptors, whose activation promotes vasoconstriction [17]. Arterioles have diameters of less than 100 μm and are characterized by a considerable drop in pressure along their path. They are the site of metabolic regulation of blood flow, as their tone is influenced by metabolites produced by surrounding cardiomyocytes [17], and express both α_1- and α_2-adrenoceptors, which induce vasoconstriction, as well as β_2-adrenoceptors, which mediate vasodilation [18–20]. Physiologically, small coronary arteries and arterioles are the main determinants of coronary vascular resistances. In healthy subjects, the overall response to a physiologic sympathetic activation is vasodilatation mainly through activation of coronary β_2-adrenoceptors. Conversely, increased cardiac sympathetic activity can induce coronary microvascular constriction, instead of the vasodilatation observed normally, in patients with endothelial dysfunction (a condition commonly found in TTS [21]), because α-adrenergic vasoconstriction becomes unrestrained and powerful enough to reduce coronary blood flow, thus contributing to myocardial ischemia [20].

Abnormal coronary vasomotion has been documented in TTS with invasive and noninvasive diagnostic tools. Using myocardial contrast echocardiography, Galiuto et al. demonstrated reversible coronary microvascular dysfunction in patients with TTS [22], with a clear perfusion defect in the dysfunctional LV segments. This perfusion defect improved transiently after intracoronary adenosine infusion, and recovered permanently over 1 month. Using positron emission tomography during the acute phase of TTS, Feola et al. demonstrated an impairment of tissue metabolism in the dysfunctional myocardium; this impairment was particularly evident in the apex and became progressively less evident in the midventricular myocardium, and disappeared at 3-month follow-up [23]. In the same study, hyperemic myocardial blood flow and coronary flow reserve were shown to be reduced in dysfunctional myocardium, and, similarly to the metabolic changes, these abnormalities recovered at 3-month follow-up. In summary, reduced contractility observed in TTS may be due, at least in part, to microvascular ischemia followed by myocardial stunning [24,25].

2.3. Catecholamine toxicity

An increase in plasma catecholamines to supra-physiological levels causes an overactivation of the β1-adrenoceptor-protein kinase-A pathway, which leads to intracellular calcium overload and oxidative stress, and ultimately cardiomyocyte necrosis and apoptosis resulting, histologically, in contraction band necrosis, which is one of the pathological hallmarks of TTS [26–29]. Catecholamine released directly into the myocardium via sympathetic nerves has been suggested to have a greater "toxic" effect than that reaching the heart via the bloodstream [30].

2.4. Activation of survival pathways

There is experimental evidence that high epinephrine levels (but not norepinephrine) [31] induce a switch in the protein coupled to β-adrenoceptors from a stimulatory protein (Gαs) to an inhibitory protein (Gαi). This switch is mediated by G-protein-coupled receptor kinase 2 and β-arrestin [32], and has been demonstrated for β_2-adrenoceptors [31], which exhibit a 35-fold higher affinity for epinephrine than for norepinephrine [33]. Interestingly, the apical LV segments have a 40% lower density of sympathetic nerve terminals [34] (which release norepinephrine), and the highest concentration of β-adrenoceptors [34] and the β2 isoform [35]. This could explain the regional difference in the response to high catecholamine levels, with circulating epinephrine having a greater influence on apical function, and the G-protein switch explaining the depression of apical contractility characteristic of TTS [35,36].

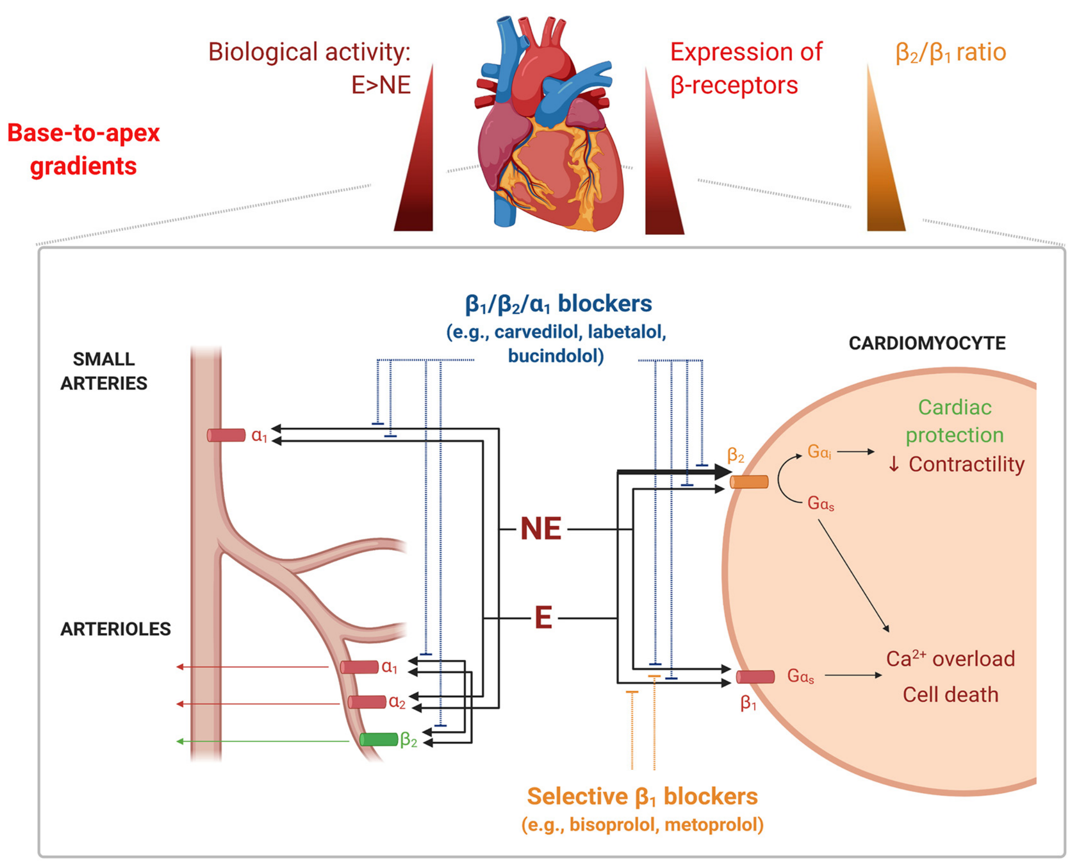

Fig. 3. Different effects of selective β_1-blockers and β_1-, β_2- and α_1-blockers on coronary vessels and cardiomyocytes. Progressing from the base to the apex of the heart, the density of sympathetic fibers (releasing norepinephrine [NE]) decreases, while the expression of β-adrenoceptors and the β_2-to-β_1 ratio increase. β_2-adrenoceptors have a much higher affinity for circulating epinephrine (E) than for NE (as shown by the thicker arrow). Therefore, the ratio between the biological activities of E and NE tends to increase from the base to the apex. The small coronary arteries express α1-adrenoceptors and the arterioles express α_1-, α_2- and β_2-adrenoceptors, while β_1- and β_2-adrenoceptors can be found on cardiomyocytes. The effects of selective β_1-blockers and non-selective, α_1-, β_1- and β_2-adrenoceptor blockers are schematically reported.

3. Rationale for β-blocker therapy in TTS

3.1. Prevention of vasospasm

As discussed above, a surge in sympathetic outflow might induce a spasm of small arteries and arterioles by activating α_1- and α_2-adrenoceptors in the context of endothelial dysfunction and atherosclerosis [20,37,38]. Therefore, the possibility exists that selective β_1-blockers might elicit vasoconstriction by shifting catecholamines toward binding to α_1 and α_2-adrenoceptos [39]. Although the use of β_1-selective agents metoprolol [6] or esmolol [9] has not been associated with severe adverse effects in TTS, β-blockers with concomitant α-blockade action such as carvedilol, labetalol or bucindolol might be preferred, as they can prevent the spasm of small arteries and arterioles [40,41].

3.2. Prevention of catecholamine toxicity

It is generally accepted that chronically elevated stimulation of the cardiac β-adrenergic system is toxic to the heart, and that cardiotoxicity is mediated by β_1-adrenoceptor activation [42]. Among the supporting evidence, there are studies on transgenic mice showing that low-level (around 5-fold) overexpression of β_1-adrenoceptor leads to early and marked cardiomyopathy, while up to 100-fold overexpression of β_2-adrenoceptors causes a significant increase in cardiac contractile force without the development of cardiac disease over 1 year [43]. In patients with HF, downregulation of β_1-adrenoceptors acts as a protective mechanism against cardiotoxicity [42]. In the acute phase of TTS, pharmacological blockade of β_1-adrenoceptors might exert a similar protective function. Drugs with combined β_1-, β_2- and α_1-blockade might prove more beneficial than selective β_1-blockers by not reversing the downregulation of β_1-adrenoceptors [44] and causing a prominent reduction of cardiac and systemic adrenergic drive [44–47], as previously demonstrated in the setting of HF.

3.3. Attenuation of the depressed myocardial contractility

As discussed above, β_2-adrenoceptor activation during the acute phase of TTS is a double-edged sword, because it induces protective depression of myocardial contractility that, however, contributes to the deterioration of ventricular function [35,36]. A selective β_1-blocker would leave β_2-adrenoceptors unblocked, and then able to mediate this cardiac protective response. β-blockers blocking both β_1- and β_2-adrenoceptors might then promote the recovery from LV dysfunction while inhibiting the detrimental β_1 activation.

4. Conclusions

Although β-blockers are often used in patients with TTS, there are no specific recommendations regarding which β-blocker agents should be preferred in individual patients [2,48]. As a consequence, it remains unclear if the best option is a selective β_1-blocker (e.g., atenolol), a β_1- and β_2-blocker (e.g., propranolol), or a β- and α_1-blocker drug (e.g., carvedilol, labetalol or bucindolol), which act as vasodilators because of their effects on α_1 adrenoceptors. Based on our current understanding of TTS pathophsiology [24,25,49], there is a rationale to prefer non-selective β-blockers with vasodilating activity over β1-selective drugs in the acute phase of TTS [50]. Although a clear-cut demonstration is lacking, we hypothesize that the reason why a β-blocker with vasodilating activity could be more effective than a selective β_1-blocker is threefold: 1) it might prevent coronary spasm even in the presence of endothelial dysfunction, 2) it might protect cardiomyocytes from catecholamine toxicity, and 3) it could relieve β_2-adrenoceptors mediated contractile dysfunction due to the G-protein switch. These mechanisms are recapitulated in Fig. 3. Nonetheless, we acknowledge that this proposal relies simply on pathophysiological considerations, and further evidence from preclinical and human studies is needed [8].

Declaration of Competing Interest

None.

References

[1] A. Prasad, G. Dangas, M. Srinivasan, J. Yu, B.J. Gersh, R. Mehran, G.W. Stone, Incidence and angiographic characteristics of patients with apical ballooning syndrome (takotsubo/stress cardiomyopathy) in the HORIZONS-AMI trial: an analysis from a multicenter, international study of ST-elevation myocardial infarction, Catheteriz. Cardiovasc. Intervent. Official J. Soc. Cardiac Angiogr. Intervent. 83 (2014) 343–348.

[2] J.R. Ghadri, I.S. Wittstein, A. Prasad, S. Sharkey, K. Dote, Y.J. Akashi, V.L. Cammann, F. Crea, L. Galiuto, W. Desmet, T. Yoshida, R. Manfredini, I. Eitel, M. Kosuge, H.M. Nef, A. Deshmukh, A. Lerman, E. Bossone, R. Citro, T. Ueyama, D. Corrado, S. Kurisu, F. Ruschitzka, D. Winchester, A.R. Lyon, E. Omerovic, J.J. Bax, P. Meimoun, G. Tarantini, C. Rihal, S. YH, F. Migliore, J.D. Horowitz, H. Shimokawa, T.F. Lüscher, C. Templin, International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology, Eur. Heart J. 39 (2018) 2032–2046.

[3] C. Templin, J.R. Ghadri, J. Diekmann, L.C. Napp, D.R. Bataiosu, M. Jaguszewski, V.L. Cammann, A. Sarcon, V. Geyer, C.A. Neumann, B. Seifert, J. Hellermann, M. Schwyzer, K. Eisenhardt, J. Jenewein, J. Franke, H.A. Katus, C. Burgdorf, H. Schunkert, C. Moeller, H. Thiele, J. Bauersachs, C. Tschöpe, H.P. Schultheiss, C.A. Laney, L. Rajan, G. Michels, R. Pfister, C. Ukena, M. Böhm, R. Erbel, A. Cuneo, K.H. Kuck, C. Jacobshagen, G. Hasenfuss, M. Karakas, W. Koenig, W. Rottbauer, S.M. Said, R.C. Braun-Dullaeus, F. Cuculi, A. Banning, T.A. Fischer, T. Vasankari, K.E. Airaksinen, M. Fijalkowski, A. Rynkiewicz, M. Pawlak, G. Opolski, R. Dworakowski, P. MacCarthy, C. Kaiser, S. Osswald, L. Galiuto, F. Crea, W. Dichtl, W.M. Franz, K. Empen, S.B. Felix, C. Delmas, O. Lairez, P. Erne, J.J. Bax, I. Ford, F. Ruschitzka, A. Prasad, T.F. Lüscher, Clinical features and outcomes of Takotsubo (Stress) cardiomyopathy, New Engl. J. Med 373 (2015) 929–938.

[4] O. De Backer, P. Debonnaire, S. Gevaert, L. Missault, P. Gheeraert, L. Muyldermans, Prevalence, associated factors and management implications of left ventricular outflow tract obstruction in takotsubo cardiomyopathy: a two-year, two-center experience, BMC Cardiovasc. Disord. 14 (2014) 147.

[5] J.R. Ghadri, I.S. Wittstein, A. Prasad, S. Sharkey, K. Dote, Y.J. Akashi, V.L. Cammann, F. Crea, L. Galiuto, W. Desmet, T. Yoshida, R. Manfredini, I. Eitel, M. Kosuge, H.M. Nef, A. Deshmukh, A. Lerman, E. Bossone, R. Citro, T. Ueyama, D. Corrado, S. Kurisu, F. Ruschitzka, D. Winchester, A.R. Lyon, E. Omerovic, J.J. Bax, P. Meimoun, G. Tarantini, C. Rihal, S. YH, F. Migliore, J.D. Horowitz, H. Shimokawa, T.F. Lüscher, C. Templin, International expert consensus document on Takotsubo syndrome (Part II): diagnostic workup, outcome, and management, Eur. Heart J. 39 (2018) 2047–2062.

[6] Y. Izumi, H. Okatani, M. Shiota, T. Nakao, R. Ise, G. Kito, K. Miura, H. Iwao, Effects of metoprolol on epinephrine-induced takotsubo-like left ventricular dysfunction in non-human primates, Hypertension Res. Off. J. Jpn. Soc. Hypertension. 32 (2009) 339–346.

[7] T. Ueyama, K. Kasamatsu, T. Hano, K. Yamamoto, Y. Tsuruo, I. Nishio, Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: a possible animal model of 'tako-tsubo' cardiomyopathy, Circul. J. Off. J. Jpn. Circul. Soc. 66 (2002) 712–713.

[8] S. YH, P. Tornvall, Reply to: metoprolol, or propranolol, or carvedilol, or labetalol, for patients with takotsubo syndrome? Clin. Autonom. Res. Off. J. Clin. Autonom. Res. Soc 28 (2018) 133–134.

[9] F. Santoro, R. Ieva, A. Ferraretti, M. Fanelli, F. Musaico, N. Tarantino, L.D. Martino, L.D. Gennaro, P. Caldarola, M.D. Biase, N.D. Brunetti, Hemodynamic effects, safety, and feasibility of intravenous esmolol infusion during Takotsubo cardiomyopathy with left ventricular outflow tract obstruction: results from a multicenter registry, Cardiovasc. Ther. 34 (2016) 161–166.

[10] T. Isogai, H. Matsui, H. Tanaka, K. Fushimi, H. Yasunaga, Early β-blocker use and in-hospital mortality in patients with Takotsubo cardiomyopathy, Heart 102 (2016) 1029–1035.

[11] S. Kumar, S. Kaushik, A. Nautiyal, S.K. Choudhary, B.L. Kayastha, N. Mostow, J.M. Lazar, Cardiac rupture in Takotsubo cardiomyopathy: a systematic review, Clin. Cardiol. 34 (2011) 672–676.

[12] K. Singh, K. Carson, Z. Usmani, G. Sawhney, R. Shah, J. Horowitz, Systematic review and meta-analysis of incidence and correlates of recurrence of Takotsubo cardiomyopathy, Int. J. Cardiol. 174 (2014) 696–701.

[13] M. Bonacchi, A. Vannini, G. Harmelin, S. Batacchi, M. Bugetti, G. Sani, A. Peris, Inverted-Takotsubo cardiomyopathy: severe refractory heart failure in poly-trauma patients saved by emergency extracorporeal life support, Interact. Cardiovasc. Thorac. Surg. 20 (2015) 365–371.

[14] F. Santoro, R. Ieva, F. Musaico, A. Ferraretti, G. Triggiani, N. Tarantino, M. Di Biase, N.D. Brunetti, Lack of efficacy of drug therapy in preventing takotsubo cardiomyopathy recurrence: a meta-analysis, Clin. Cardiol. 37 (2014) 434–439.

[15] J.H. Coote, R.A. Chauhan, The sympathetic innervation of the heart: important new insights, Autonom. Neurosci. Basic Clin. 199 (2016) 17–23.

[16] G.L. Todd, G. Baroldi, G.M. Pieper, F.C. Clayton, R.S. Eliot, Experimental catecholamine-induced myocardial necrosis. I. Morphology, quantification and

regional distribution of acute contraction band lesions, J. Mol. Cell. Cardiol. 17 (1985) 317–338.
[17] P.G. Camici, O.E. Rimoldi, F. Crea, Coronary microvascular dysfunction, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 11th editionElsevier, 2018.
[18] R.A. Cohen, J.T. Shepherd, P.M. Vanhoutte, Prejunctional and postjunctional actions of endogenous norepinephrine at the sympathetic neuroeffector junction in canine coronary arteries, Circ. Res. 52 (1983) 16–25.
[19] W.M. Chilian, Functional distribution of alpha 1- and alpha 2-adrenergic receptors in the coronary microcirculation, Circulation. 84 (1991) 2108–2122.
[20] G. Heusch, D. Baumgart, P. Camici, W. Chilian, L. Gregorini, O. Hess, C. Indolfi, O. Rimoldi, Alpha-adrenergic coronary vasoconstriction and myocardial ischemia in humans, Circulation. 101 (2000) 689–694.
[21] M. Naegele, A.J. Flammer, F. Enseleit, S. Roas, M. Frank, A. Hirt, P. Kaiser, S. Cantatore, C. Templin, G. Fröhlich, M. Romanens, T.F. Lüscher, F. Ruschitzka, G. Noll, I. Sudano, Endothelial function and sympathetic nervous system activity in patients with Takotsubo syndrome, Int. J. Cardiol. 224 (2016) 226–230.
[22] L. Galiuto, A.R. De Caterina, A. Porfidia, L. Paraggio, S. Barchetta, G. Locorotondo, A.G. Rebuzzi, F. Crea, Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in apical ballooning or Tako-Tsubo syndrome, Eur. Heart J. 31 (2010) 1319–1327.
[23] M. Feola, S. Chauvie, G.L. Rosso, A. Biggi, F. Ribichini, M. Bobbio, Reversible impairment of coronary flow reserve in takotsubo cardiomyopathy: a myocardial PET study, J. Nucl. Cardiol. Off. Publ. Am. Soc. Nucl. Cardiol. 15 (2008) 811–817.
[24] F. Pelliccia, J.C. Kaski, F. Crea, P.G. Camici, Pathophysiology of Takotsubo syndrome, Circulation. 135 (2017) 2426–2441.
[25] A.R. Lyon, R. Citro, B. Schneider, O. Morel, J.R. Ghadri, C. Templin, E. Omerovic, Pathophysiology of Takotsubo syndrome: JACC state-of-the-art review, J. Am. Coll. Cardiol. 77 (2021) 902–921.
[26] C. Basso, G. Thiene, The pathophysiology of myocardial reperfusion: a pathologist's perspective, Heart 92 (2006) 1559–1562.
[27] H.M. Nef, H. Möllmann, C. Troidl, S. Kostin, S. Voss, P. Hilpert, C.B. Behrens, A. Rolf, J. Rixe, M. Weber, C.W. Hamm, A. Elsässer, Abnormalities in intracellular $Ca2+$ regulation contribute to the pathomechanism of Tako-Tsubo cardiomyopathy, Eur. Heart J. 30 (2009) 2155–2164.
[28] Y. Shao, B. Redfors, M. Ståhlman, M.S. Täng, A. Miljanovic, H. Möllmann, C. Troidl, S. Szardien, C. Hamm, H. Nef, J. Borén, E. Omerovic, A mouse model reveals an important role for catecholamine-induced lipotoxicity in the pathogenesis of stress-induced cardiomyopathy, Eur. J. Heart Fail. 15 (2013) 9–22.
[29] M. Wallner, J.M. Duran, S. Mohsin, C.D. Troupes, D. Vanhoutte, G. Borghetti, R.J. Vagnozzi, P. Gross, D. Yu, D.M. Trappanese, H. Kubo, A. Toib, T.E. Sharp 3rd, S.C. Harper, M.A. Volkert, T. Starosta, E.A. Feldsott, R.M. Berretta, T. Wang, M.F. Barbe, J.D. Molkentin, S.R. Houser, Acute catecholamine exposure causes reversible myocyte injury without cardiac regeneration, Circ. Res. 119 (2016) 865–879.
[30] W. Raab, E. Stark, W.H. Macmillan, W.R. Gigee, Sympathogenic origin and antiadrenergic prevention of stress-induced myocardial lesions, Am. J. Cardiol. 8 (1961) 203–211.
[31] J.F. Heubach, U. Ravens, A.J. Kaumann, Epinephrine activates both Gs and Gi pathways, but norepinephrine activates only the Gs pathway through human beta2-adrenoceptors overexpressed in mouse heart, Mol. Pharmacol. 65 (2004) 1313–1322.
[32] T. Nakano, K. Onoue, Y. Nakada, H. Nakagawa, T. Kumazawa, T. Ueda, T. Nishida, T. Soeda, S. Okayama, M. Watanabe, H. Kawata, R. Kawakami, M. Horii, H. Okura, S. Uemura, K. Hatakeyama, Y. Sakaguchi, Y. Saito, Alteration of β-adrenoceptor signaling in left ventricle of acute phase Takotsubo syndrome: a human study, Sci. Rep. 8 (2018) 12731.
[33] C. Hoffmann, M.R. Leitz, S. Oberdorf-Maass, M.J. Lohse, K.N. Klotz, Comparative pharmacology of human beta-adrenergic receptor subtypes–characterization of stably transfected receptors in CHO cells, Naunyn Schmiedeberg's Arch. Pharmacol. 369 (2004) 151–159.
[34] H. Mori, S. Ishikawa, S. Kojima, J. Hayashi, Y. Watanabe, J.I. Hoffman, H. Okino, Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli, Cardiovasc. Res. 27 (1993) 192–198.
[35] H. Paur, P.T. Wright, M.B. Sikkel, M.H. Tranter, C. Mansfield, P. O'Gara, D.J. Stuckey, V.O. Nikolaev, I. Diakonov, L. Pannell, H. Gong, H. Sun, N.S. Peters, M. Petrou, Z. Zheng, J. Gorelik, A.R. Lyon, S.E. Harding, High levels of circulating epinephrine trigger apical cardiodepression in a β2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy, Circulation. 126 (2012) 697–706.
[36] A.R. Lyon, P.S. Rees, S. Prasad, P.A. Poole-Wilson, S.E. Harding, Stress (Takotsubo) cardiomyopathy–a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning, Nat. Clin. Pract. Cardiovasc. Med. 5 (2008) 22–29.
[37] G. Heusch, A. Deussen, J. Schipke, V. Thämer, Alpha 1- and alpha 2-adrenoceptor-mediated vasoconstriction of large and small canine coronary arteries in vivo, J. Cardiovasc. Pharmacol. 6 (1984) 961–968.
[38] J.A. Vita, C.B. Treasure, A.C. Yeung, V.I. Vekshtein, G.M. Fantasia, R.D. Fish, P. Ganz, A.P. Selwyn, Patients with evidence of coronary endothelial dysfunction as assessed by acetylcholine infusion demonstrate marked increase in sensitivity to constrictor effects of catecholamines, Circulation. 85 (1992) 1390–1397.
[39] Y. Tamura, K. Sakata, M.A. Kawashiri, M. Yamagishi, Multi-vessel coronary vasospasm after beta-blocker administration, Intern. Med. (Tokyo, Japan) 57 (2018) 3219–3220.
[40] D. Tzivoni, A. Keren, J. Benhorin, S. Gottlieb, D. Atlas, S. Stern, Prazosin therapy for refractory variant angina, Am. Heart J. 105 (1983) 262–266.
[41] M.D. Winniford, N. Filipchuk, L.D. Hillis, Alpha-adrenergic blockade for variant angina: a long-term, double-blind, randomized trial, Circulation. 67 (1983) 1185–1188.
[42] R.J. Lefkowitz, H.A. Rockman, W.J. Koch, Catecholamines, cardiac beta-adrenergic receptors, and heart failure, Circulation. 101 (2000) 1634–1637.
[43] S.B. Liggett, N.M. Tepe, J.N. Lorenz, A.M. Canning, T.D. Jantz, S. Mitarai, A. Yatani, G.W. Dorn 2nd., Early and delayed consequences of beta(2)-adrenergic receptor overexpression in mouse hearts: critical role for expression level, Circulation. 101 (2000) 1707–1714.
[44] E.M. Gilbert, W.T. Abraham, S. Olsen, B. Hattler, M. White, P. Mealy, P. Larrabee, M.R. Bristow, Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart, Circulation. 94 (1996) 2817–2825.
[45] E.M. Gilbert, J.L. Anderson, D. Deitchman, F.G. Yanowitz, J.B. O'Connell, D.G. Renlund, M. Bartholomew, P.C. Mealey, P. Larrabee, M.R. Bristow, Long-term beta-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind, randomized study of bucindolol versus placebo, Am. J. Med. 88 (1990) 223–229.
[46] M.R. Bristow, P. Larrabee, W. Minobe, R. Roden, L. Skerl, J. Klein, D. Handwerger, J.D. Port, B. Müller-Beckmann, Receptor pharmacology of carvedilol in the human heart, J. Cardiovasc. Pharmacol. 19 (Suppl. 1) (1992) S68–S80.
[47] M.R. Bristow, R.L. Roden, B.D. Lowes, E.M. Gilbert, E.J. Eichhorn, The role of third-generation beta-blocking agents in chronic heart failure, Clin. Cardiol. 21 (1998) I3–13.
[48] A.R. Lyon, E. Bossone, B. Schneider, U. Sechtem, R. Citro, S.R. Underwood, M.N. Sheppard, G.A. Figtree, G. Parodi, Y.J. Akashi, F. Ruschitzka, G. Filippatos, A. Mebazaa, E. Omerovic, Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology, Eur. J. Heart Fail. 18 (2016) 8–27.
[49] L. Boussel, G. Herigault, A. de la Vega, M. Nonent, P.C. Douek, J.M. Serfaty, Swallowing, arterial pulsation, and breathing induce motion artifacts in carotid artery MRI, J. Magnetic Reson. Imaging JMRI. 23 (2006) 413–415.
[50] J.E. Madias, Metoprolol, propranolol, carvedilol, or labetalol for patients with Takotsubo syndrome? Clin. Autonom. Res. Off. J. Clin. Autonom. Res. Soc. 28 (2018) 131–132.