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

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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 β1-selective drugs.

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 β1-blocker) [6], or amosulalol (a drug with a much higher affinity for α1-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...
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

### Table 1

The International Takotsubo (InterTAK) diagnostic criteria.

<table>
<thead>
<tr>
<th>Mild TTS with or without signs of HF</th>
<th>HF/pulmonary edema</th>
<th>Hypotension/ cardiogenic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider:</strong></td>
<td><strong>Consider:</strong></td>
<td><strong>Consider:</strong></td>
</tr>
<tr>
<td>- ACE/ARB</td>
<td>- ACE/ARB</td>
<td>- LV fluid (if no HF)</td>
</tr>
<tr>
<td>- β-blockers</td>
<td>- β-blockers</td>
<td>- Short-acting β-blocker</td>
</tr>
<tr>
<td><strong>Avoid:</strong></td>
<td>- Diuretics (if no LVOTO)</td>
<td>- LVAD (Impella)</td>
</tr>
<tr>
<td>- loop diuretics</td>
<td>- Nitroglycerin (if no LVOTO)</td>
<td>- VA-ECMO</td>
</tr>
<tr>
<td>- loop diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arrhythmias</strong></td>
<td><strong>Thrombosis/embolism</strong></td>
<td></td>
</tr>
<tr>
<td>- β-blockers</td>
<td><strong>Consider:</strong></td>
<td><strong>Consider:</strong></td>
</tr>
<tr>
<td>- Temporary RV pacing if AV block</td>
<td>- Heparin/VKA/NOAC (until first FU)</td>
<td>- Consider anticoagulation if LVEF ≤30% and/or large</td>
</tr>
<tr>
<td>- Life Vest</td>
<td>- Consider anticoagulation if LVEF ≤30% and/or large</td>
<td></td>
</tr>
<tr>
<td><strong>Avoid:</strong></td>
<td>LV dysfunction involving the apex</td>
<td></td>
</tr>
<tr>
<td>- QT-interval prolonging drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- β-blockers in pts with bradycardia + Qtc &gt;500 ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Permanent devices</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3 months or until RWMA recovery</strong></td>
<td><strong>Treatment of underlying disorder</strong></td>
<td><strong>Recurrence prevention</strong></td>
</tr>
<tr>
<td><strong>Consider:</strong></td>
<td><strong>Consider:</strong></td>
<td><strong>Consider:</strong></td>
</tr>
<tr>
<td>- ACE/ARB</td>
<td>- CAD:</td>
<td>- Hormone replacement therapy</td>
</tr>
<tr>
<td></td>
<td>- Aspirin</td>
<td>- ACE/ARB</td>
</tr>
<tr>
<td></td>
<td>- Statin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Depression/anxiety:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Specific treatment</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Recommendations on the management of Takotsubo syndrome (TTS). ACE/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].

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*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.
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].
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 123I-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 α1-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 α1- and α2-adrenoceptors, which induce vasoconstriction, as
well as $\beta_2$-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 $\beta_2$-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 $\alpha$-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 $\beta_1$-adrenoceptor-protein kinase-A pathway, which leads to intracellular calcium overload and oxidative stress, and ultimately cardiomyocyte necrosis and apoptosis resulting, histo- logically, 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 $\beta$-adrenoceptors from a stimulatory protein ($G_\alpha_s$) to an inhibitory protein ($G_\alpha_i$). This switch is mediated by G-protein-coupled receptor kinase 2 and $\beta$-arrestin [32], and has been demonstrated for $\beta_2$-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 $\beta$-adrenoceptors [34] and the $\beta_2$ 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].

![Diagram](https://example.com/diagram.png)

Fig. 3. Different effects of selective $\beta_1$-blockers and $\beta_1$, $\beta_2$-, and $\alpha_1$-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 $\beta$-adrenoceptors and the $\beta_2$-to-$\beta_1$ ratio increase. $\beta_2$-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 $\alpha_1$-adrenoceptors and the arterioles express $\alpha_1$, $\alpha_2$, and $\beta_2$-adrenoceptors, while $\beta_1$- and $\beta_2$-adrenoceptors can be found on cardiomyocytes. The effects of selective $\beta_1$-blockers and non-selective, $\alpha_1$, $\beta_1$, and $\beta_2$-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 α1- and α2-adrenoceptors in the context of endothelial dysfunction and atherosclerosis [20,37,38]. Therefore, the possibility exists that selective β1-blockers might elicit vasconstriction by shifting catecholamines toward binding to α1 and α2-adrenoceptors [39]. Although the use of β1-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 β1-adrenoceptor activation [42]. Among the supporting evidence, there are studies on transgenic mice showing that low-level (around 5-fold) overexpression of β1-adrenoceptor leads to early and marked cardiomyopathy, while up to 100-fold overexpression of β2-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 β2-adrenoceptors acts as a protective mechanism against cardiotoxicity [42]. In the acute phase of TTS, pharmacological blockade of β2-adrenoceptors might exert a similar protective function. Drugs with combined β1-, β2- and α1-blockade might prove more beneficial than selective β1-blockers by not reversing the downregulation of β1-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, β2-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 β1-blocker would leave β2-adrenoceptors unblocked, and then able to mediate this cardiac protective response. β-blockers blocking both β2- and β1-adrenoceptors might then promote the recovery from LV dysfunction while inhibiting the detrimental β1-activation.

4. Conclusions

Although β1-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 β1-blocker (e.g., atenolol), a β1- and β2-blocker (e.g., propranolol), or a β1- and α1-blocker drug (e.g., carvedilol, labetalol or bucindolol), which act as vasodilators because of their effects on α1-adrenoceptors. Based on our current understanding of TTS pathophysiology [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 β1-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 β2-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


