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Is ivabradine suitable to control undesirable tachycardia induced by dobutamine in cardiogenic shock treatment?

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ABSTRACT

Inotropic treatment remains the cornerstone for cardiogenic shock, an emergency that requires immediate resuscitative therapy before shock irreversibly damages vital organs. Although the sympathomimetic drug dobutamine is the most widely-used inotropic drug worldwide, it has several side effects including sinus tachycardia. Dobutamine partly restores systolic heart failure (HF); however, it increases the heart rate (HR) which counterbalances the beneficial effects. Ivabradine, a new selective I_f inhibitor, provides specific HR reduction and is indicated in stable coronary artery disease and in stable chronic HF with left ventricular dysfunction. Despite scarce data indicating beneficial effects of ivabradine in sinus tachycardia in various clinical settings, this drug remains contraindicated in acute HF. We propose that ivabradine could help to prevent the dobutamine-induced side effects, and that their combination in clinical practice could lead to pure inotropic effects, useful for the management of cardiogenic shock.

Background

The Guidelines for the Diagnosis and Management of heart failure (HF) from the American College of Cardiology/American Heart Association for the management of acute HF recommend limited use of the inotropic agents, however, "intravenous inotropic drugs such as dopamine, dobutamine or milrinone might be reasonable for those patients presenting with documented severe systolic dysfunction, low blood pressure and evidence of low cardiac output, with or without congestion, to maintain systemic perfusion and preserve end-organ performance" [1]. These guidelines explicitly state that intravenously administered positive inotropic agents are not recommended for hospitalized patients with HF who do not have evidence of decreased organ perfusion. The recent guidelines of the European Society of Cardiology also recommend limited use of inotropic agents and highlight the inotrope-induced tachycardia in acute HF [2]: "use of an inotrope such as dobutamine should usually be reserved for patients with such severe reduction in cardiac output that vital organ perfusion is compromised. Such patients are almost always hypotensive ('shocked'). Inotropes cause sinus tachycardia and may induce myocardial ischemia and arrhythmias. There is long-standing concern that they may increase mortality." Although the effect of these drugs is not established with regards to mortality, they are paradoxically given in life-threatening situations. These patients have a poor prognosis and specific clinical trials are difficult to initiate.

Given the poor clinical evidence and non-specific recommendations, the use of inotropic agents is not consistent among clinical practices [3]. The risk-standardized rates of inotrope use ranged from 0.9% to 44.6% (median: 6.3%, interquartile range: 4.3–9.2%) across 376 hospitals with 189,948 hospitalizations for HF from 2009 through 2010 in USA. Variable therapies were also observed between hospitals, including dobutamine alone or in combination (dobutamine-predominant in 29% of hospitals and mixed dobutamine and dopamine in 32% of hospitals) or dopamine (predominant in 25%).

Although the first clinical studies reported only mild or no tachycardia during acute intravenously dobutamine infusion in acute HF [4], tachycardia has now been consistently observed in experimental models following catecholamine infusions [5] and is widely admitted in clinical settings [6]. The dobutamine-mediated

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor antagonist; BPM, beats per minute; HCN, hyperpolarization-activated cyclic nucleotide-gated cation channels; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MODS, multiple organ dysfunction syndrome; MRA, mineralocorticoid receptor antagonist.

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tachycardic effects are most often observed in randomized trials. For example, an increase of roughly 10 bpm was reported in 18 dobutamine-treated patients [7], with HR remaining unchanged in more than 50 patients [8].

In this article, we propose alternative therapeutic avenues to improve the outcomes in the patients with cardiogenic shock requiring inotropic treatments. Ivabradine, a specific bradycardic drug could limit the dobutamine-induced tachycardia, so that the combination could provide a pure positive inotropic treatment for the management of patients with cardiogenic shock.

Dobutamine-induced tachycardia

Induced tachycardia could be the main determinant of a sustained vicious circle following dobutamine use for the treatment of cardiogenic shock (see Fig. 1). Indeed, as regards specifically sinus node, dobutamine has been shown to induce dose-related decreases in sinus cycle length, sinus node recovery time, corrected sinus node recovery time, promoting sinus tachycardia [9]. It could lead to loss of the beneficial effect of the drug on cardiac function by hampering filling. Indeed, tachycardia could first help to maintain outflow, but when filling is impaired, this physiological adaptation is not sufficient and could even be deleterious. The cut-off between these two effects is unknown and could depend on the characteristics of each patient, especially hemodynamic conditions and comorbidities. Furthermore, in a normal heart, inotropism is known to increase following increases in HR. However, this effect might be lost following cardiogenic shock, which is associated with compromised inotropism.

Finally, tachycardia could directly induce deleterious remodeling. On contrary, many evidences show that a drug, such as ivabradine, that is able to reduce HR in patients with stable HF could lead to favourable left ventricular remodeling as demonstrated, in particular, in the echographic analyses of the SHIfT study [10].

Could ivabradine, a selective HR-lowering agent, be beneficial for sinus tachycardia?

Ivabradine has been found to specifically block hyperpolarization-activated cyclic nucleotide-gated (HCN) channels without any effects on other receptors or channels in the cardiovascular system, at therapeutic concentrations (for more details, see the recent review [11]). Ivabradine inhibits the *If* funny current (supported by the HCN channels), an ionic current involved in pacemaker activity in the sinoatrial node [11–14]. *If* contributes to a depolarizing current that drives the spontaneous diastolic depolarization needed to trigger a subsequent action potential, with modulation of *If* being important in the physiological regulation of HR. HCN channels are specifically expressed in the heart and the central nervous system and ivabradine reduces HR without depressing myocardial contractility or reducing cardiac output [15,16].

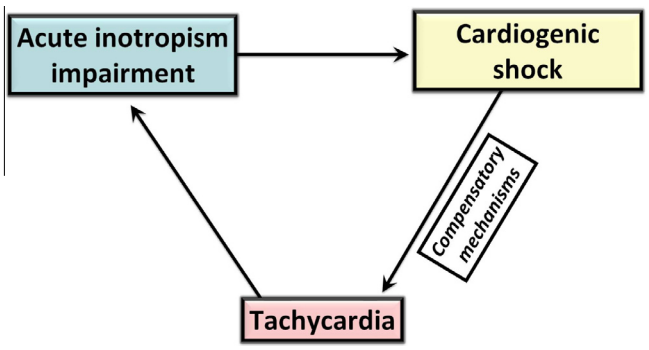

Fig. 1. Vicious circle induced by dobutamine-induced tachycardia.

By contrast, currently used drugs such as beta-blockers efficiently reduce HR, but their use is limited by adverse reactions such as erectile dysfunction, Raynaud syndrome, asthma exacerbation and so on.

Ivabradine was recently recommended (class IIa, level B) in chronic stable HF in patients in sinus rhythm with a left ventricular ejection fraction (LVEF) $\leqslant$35%, an HR $\geqslant$70 bpm, and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), angiotensin-converting enzyme (ACE) inhibitor (or angiotensin II receptor blockers (ARB)), and a mineralocorticoid receptor antagonist (MRA) [2]. In addition, ivabradine is indicated in patients with stable coronary disease with uncontrolled angina [17–20]. Nevertheless, due to lack of data, ivabradine is contraindicated in case of acute HF and cardiogenic shock, as these situations were previously defined as exclusion criteria in almost all clinical trials with ivabradine.

The hypothesis

Efficacy of ivabradine in sinus tachycardia

The effects of ivabradine on sinus tachycardia have already been tested in heart transplant recipients [21]. Because of heart denervation, sinus tachycardia is frequently observed in transplant recipients, and ivabradine appears as an interesting treatment option [22,23]. For example, ivabradine was well tolerated with no substantial adverse effect in 15 transplanted patients (in addition to β-blockers in 4 patients and on account of contraindication of β-blocker therapy in the remaining 11) [24]. Maximum drug dosage in all patients achieved a reduction in basal HR of 33 ± 6.2 bpm. Although all patients reported substantial clinical improvement, and demonstrated an increase in functional class, transplantation was the main cause of improvement.

Feasibility and tolerance of the ivabradine treatment for inappropriate sinus tachycardia has also been proposed. However, significant prospective data are currently lacking. Indeed, a study in 18 patients with a typical history of inappropriate sinus tachycardia showed that HR was significantly reduced by ivabradine [25]. Stress test indicated an increased tolerance to physical stress, with a progressive increase of maximal load reached. Ivabradine has also been suggested to alleviate postural orthostatic tachycardia syndrome (POTS: a syndrome associated with tachycardia on orthostasis-related symptoms). In a retrospective study of 20 patients, 8 patients reported reduced tachycardia and fatigue, 4 only reduced tachycardia [26] and 6 patients no efficacy (and 2 discontinuations).

Considering sinus tachycardia as a side effect of dobutamine that we could control by using ivabradine, we propose that the drug could break the vicious circle as presented in the Figs. 1 and 2.

Evaluation of the hypothesis

To our knowledge, except for MODIfY (NCT01186783), which is a prospective, single center, open label, randomized, controlled two arms, phase II-trial that will evaluate the ability of ivabradine to reduce an elevated HR in multiple organ dysfunction syndrome (MODS) patients, no prospective study is currently registered to specifically evaluate the interest of ivabradine in patients with dobutamine-induced tachycardia. However, a few clinical cases are currently available.

More specifically in patients with cardiogenic shock, clinical management is often difficult and tachycardia remains a