Does ivabradine balance dobutamine effects in cardiogenic shock? A promising new strategy

Mariama Akodad, P. Lim, François Roubille

Does ivabradine balance dobutamine effects in cardiogenic shock? A promising new strategy

See related article: Bakkehaug, J.P., Naesheim, T., Torgersen Engstad, E., Kildal, A.B., Myrmel, T. & How, O.J. 2016. Reversing dobutamine induced tachycardia using ivabradine increases stroke volume with neutral effect on cardiac energetics in left ventricular postischaemia dysfunction.

Cardiogenic shock (CS) is associated with a high rate of in-hospital mortality and a poor prognosis. Inotropic agents, used in clinical practice, remain the cornerstone of the management of CS. Dobutamine is the most usually preferred in this indication. Despite its benefit effects, this drug also exerts adverse effects as sinus tachycardia, possibly deleterious in this context. In the recent ESC guidelines (Ponikowski *et al.* 2016), inotropic agents are clearly not recommended for the management of a patient with acute HF unless the patient is symptomatically hypotensive or hypoperfused because of safety concern (class III, A). Short-term, intravenous infusion of inotropic agents may be considered in patients with hypotension (SBP < 90 mmHg) and/or signs of hypoperfusion (despite adequate volemia), in order to maintain and improve the cardiac outflow, peripheral perfusion and maintain end-organ function (class IIb, level C). Dobutamine has even been suggested to increase mortality (O'Connor *et al.* 1999, Wang *et al.* 2015).

The level of recommendation and the years of publications of main trials in the field underline that we lack data, regarding both basic models and clinical trials.

We lack strong clinical data in the field. Only few trials are currently studying CS (Table 1). As indicated in the Table 1, there are some epidemiological or prognostic evaluations, some trials on mechanical assistances and devices, but surprisingly few studies with drugs (and none evaluating ivabradine in this context to our knowledge). A few years ago, the interest of intra-aortic balloon support for patients with acute myocardial infarction leading to CS has been definitely challenged (Thiele *et al.* 2012, 2013), reinforcing the lack of trials and recommendations with strong level of evidence.

Even epidemiological data are rather scarce and local uses are heterogeneous. Recently, a multi-centre study (Harjola *et al.* 2015) included in nine centres representing eight countries. A total of 219 patients were included over 2 years, underlining the high difficulties to conduct a trial in the field. Consistently, FRENCHSHOCK, a French nationwide registry, is currently ongoing (NCT02703038). Its aim is to reflect the current practice in the field, including the likely heterogeneous clinical strategies, in a nationwide registry, in the as short as possible framework (>500 patients in less than 6 months).

Importantly, this registry aims to present real-life clinical features and management of more than 500 patients in various centres. The current management of CS is indeed crucial including the real use of inotropic drugs and their prognostic impact.

We lack basic data in the field. In the study published in this journal, Bakkehaug *et al.* (2016) reported a basic model of CS (Bakkehaug *et al.* 2016).

The aim of the authors was to evaluate the effect of a combined therapy by dobutamine and ivabradine in a model of post-ischaemic low cardiac output.

Indeed, both inotropic impact and induced tachycardia by dobutamine participate to increase the cardiac output in CS. On the other hand, the induced sinus tachycardia could exert in turn deleterious effects (we could also cite other side effects such as arrhythmias). Indeed, increased tachycardia may increase left ventricular work inducing myocardial ischaemia and shortening diastole period and then efficient ventricular filling.

Ivabradine is a specific blocker of the If funny current supported by the hyperpolarization-activated cyclic nucleotide-gated channels. This ionic current is involved in activity of the sinoatrial node. The interest of ivabradine is the reduction of heart rate without depressing myocardial inotropism or decreasing cardiac output (Roubille & Tardif 2013). This reduction remains mild (about 9 bpm in the clinical trials in patients with HF), which appears compatible with haemodynamics adaptation and not compromising this adaptive tentative, hence its theoretical interest in this setting (Roubille *et al.* 2013, Lattuca & Roubille 2015).

Ivabradine is currently indicated in chronic heart failure (class IIa, level B), in patients in sinus rhythm with a left ventricular ejection fraction <35% and heart rate <70% despite treatment with an evidence-based dose of beta-blockers, angiotensin-converting enzyme inhibitor and a mineralo-corticoid receptor antagonist (Ponikowski *et al.* 2016). Importantly, it is currently not recommended in patients with acute HF as no randomized large trials addressed this issue. Only few data are available concerning its indication in CS.

Table I Ongoing trials as regards cardiogenic shock

Country	Intervention	Primary endpoint	Main objective	Number of patients	Results available	NCT
Epidemiology, prognostic stratification						
France	Registry	Observatory	Current practice in a nationwide register	500	2017	NCT02703038
Spain	Observatory	Mortality	Prognostic value of circulating microRNAs in patients with STEMI complicated by CS			NCT02691286
Mechanical treatments						
Czech republic	ECLS	30-day composite of death from any cause, resuscitated circulatory arrest and implantation of another mechanical circulatory support device	Immediate veno-arterial ECMO versus early conservative therapy according to standard practice	120	2019	NCT02301819
Europe	HeartMate®	Safety and efficiency: clinical stabilization at H72 defined as improvement of cardiac index to > 2.2 L/min/m^2	HeartMate PHP® to provide haemodynamic support for up to 72 h in patients with CC requiring stabilization.	25	2017	NCT02279979
Denmark	Impella® cVAD	>6 months of death from all causes	Impella® device versus standard therapy	360	2018	NCT01633502
France	ECLS+/−hypothermia	30-day all-cause mortality	Randomization for hypothermia	334	2020	NCT02754193
Germany	ECLS	LVEF on day 30	ECLS versus standard therapy in patients with CS complicating AMI	42	2019	NCT02544594
New management avenues						
Italy	Epinephrine	Day 60 mortality.	IV epinephrine infusion as an early and fast haemodynamic stabilizer	24	2017	NCT02591771
France	Epinephrine/ norepinephrine	Cardiac index until release from ICU	IV epinephrine or norepinephrine prepared in syringes in order to obtain a MAP of 65–70 mmHg	80	2017	NCT01367743

Table 1 (continued)

Country	Intervention	Primary endpoint	Main objective	Number of patients	Results available	NCT
Germany	Hypothermia	Cardiac power index after 24 h	Mild hypothermia for 24 h with invasive cooling in addition to PCI and OMT versus PCI and OMT	40	2016	NCT01890317
China		Anti-inflammatory impact (TNF-α, IL-1 β, IL-6, IL-10)	Therapeutic hypothermia (33–34°C)	50	2017	NCT02633358
Germany	PCI	30-day mortality and/or severe renal failure requiring renal replacement therapy	Immediate multi-vessel versus culprit vessel only angioplasty	706	2017	NCT01927549

AMI, acute myocardial infarction; CS, cardiogenic shock; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; IV, Intravenous; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
84 studies are registered on 'clinicaltrials.gov' on May 2016 (when discard the studies terminated (n = 37) , withdrawn (n = 2) or when status remains unknown (n = 10). Only trials including patients exclusively with CC requiring medical management are presented (for instance patients benefiting from a PCI at high risk or in a surgical context are not presented).

Bakkehaug *et al.* (2016) proposed a double approach to assess the effects of this pure negative chronotropic drug without inotropic depression in the context of CS:

1 They firstly studied the interest of ivabradine in a large-animal model. An ischaemia–reperfusion protocol was performed in 12 pigs after intermittent ligation of the left coronary arteries under general anaesthesia. Haemodynamic and energetic measurements by intracardiac catheterism and sonomicrometry crystals were performed to assess several data, mainly heart rate, cardiac output, stroke volume, stroke work, myocardial oxygen consumption, end left ventricular systolic and end-diastolic dimension and diastolic filling time.

Effects of a treatment regimen compounded only with dobutamine on these parameters were compared to the combination of dobutamine–ivabradine.

Introduction of dobutamine in post-ischaemic heart (5 μg kg^{-1} min^{-1}) increased cardiac output by increasing significantly heart rate from 102 ± 21 to 131 ± 16 bpm ($P < 0.05$).

The analysis demonstrated that an adjunction of ivabradine in the pigs treated with dobutamine permitted to decrease heart rate to the baseline (100 ± 9 bpm) without any effect on cardiac output or blood pressure.

The second main result was the positive impact of ivabradine on stroke volume, from 30 ± 5 to 36 ± 5 mL ($P < 0.05$) mainly by increasing the diastolic filling and the end-diastolic dimensions. No effect was found concerning the myocardial energetic consumption.

2 They confirmed the data obtained in the first model in a second model of heart of *ex vivo* mice using a Langendorff model. Hearts of 16 mice were removed and a 40 min of ischaemia was performed followed by 5 min of reperfusion. Isoproterenol was used, increasing myocardial oxygen consumption and cardiac output, similarly due to an elevation of heart rate. Ivabradine was then added and permitted to return the heart rate to baseline reducing myocardial oxygen consumption. The stroke volume tended to increase (P = ns).

This study is innovative in the field of CS and shows by two different protocols and in two different animal models (rodent and pig) a benefit of ivabradine as regards haemodynamic parameters.

The main limit is that measurement was taken in stable haemodynamic conditions which is difficult to extend to clinical practice with most of time unstable patients.

Ivabradine is well known to exert positive effects in the context of stable heart failure by decreasing heart rate and then myocardial oxygen consumption and is indicated in this context (Ponikowski *et al.* 2016).

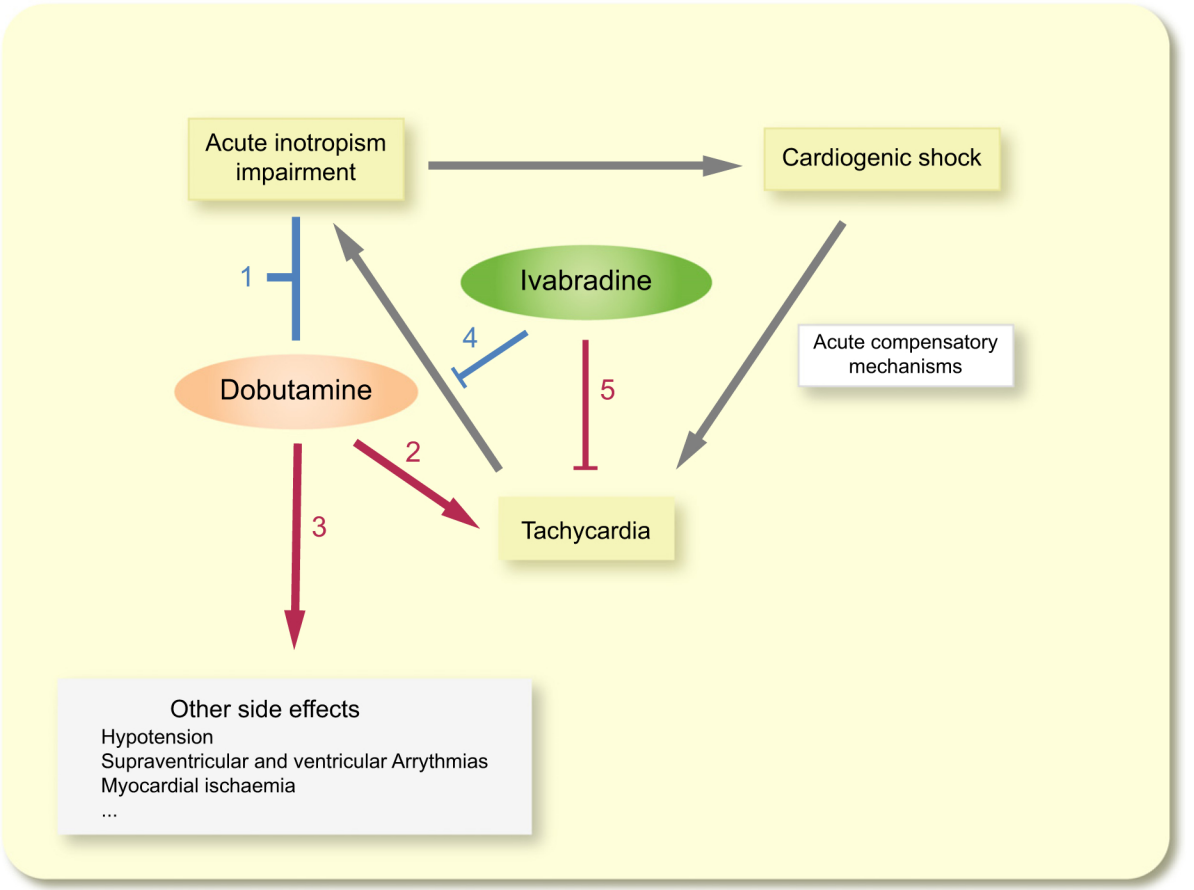

Figure 1 Schematic presentation of the theoretical interest of ivabradine in cardiogenic shock. Initial contractility and inotropism failure lead to cardiogenic shock and induce compensatory mechanisms such as increased heart rate to maintain effective cardiac output. As a side effect, this compensatory phenomenon results in an increase in oxygen consumption and decrease in systolic ejection volume, leading to a vicious circle. On the one hand, the introduction of dobutamine could restore inotropism [1]. On the other hand, it could participate in tachycardia leading to diastolic impairment [2,3]. The combined use of a pure heart rate lowering agent such as ivabradine would limit this increase in heart rate and then break the vicious circle [4,5]. Adapted from Lattuca and Roubille (2015).

In the context of CS treated with dobutamine, ivabradine could exert a beneficial effect regarding to the decrease in heart rate, reducing also arrhythmias, myocardial ischaemia and potentially myocardial energetic consumption (Fig. 1).

Clinical trials are difficult to initiate in patients with CS due mainly to their unstable status and high rate of mortality. In a recent paper, the authors reported promising data by adding ivabradine 5 mg twice daily in patients treated with dobutamine infusion for a refractory CS ($n = 9$) (Gallet *et al.* 2014). They showed that ivabradine allowed to improve diastolic filling time without decreasing cardiac output. At 24 h, an increase in systolic blood pressure, daily urine output, oxygen balance and NT-proBNP level was noticed. This pilot study highlighted the safety and a potential benefit of ivabradine in the context of CS under inotropic support.

In conclusion, results presented in the paper of Bakkehaug *et al.* (2016) are promising and have to be confirmed by a clinical study to assess the effect of this strategy in the aim to counteract deleterious effects of dobutamine in patients with CS all the more as we lack data and because of poor outcomes in this setting.

Conflicts of interest

FR received honoraria for lectures by Servier, Novartis and received research grants by Servier, Novartis.

M. Akodad,[1,2] *P. Lim*[3] *and F. Roubille*[1,2]
[1]Cardiology Department, University Hospital of Montpellier, Montpellier, France
[2]PhyMedExp, INSERM U1046, CNRS UMR 9214, University of Montpellier,

Montpellier Cedex 5, France
[3]Cardiology Intensive Care, University Hospital Henri Mondor, Créteil, France
E-mail: francois.roubille@gmail.com

References

Bakkehaug, J.P., Naesheim, T., Torgersen Engstad, E., Kildal, A.B., Myrmel, T. & How, O.J. 2016. Reversing dobutamine induced tachycardia using ivabradine increases stroke volume with neutral effect on cardiac energetics in left ventricular postischaemia dysfunction. *Acta Physiol (Oxf)* **218**, 78–88.

Gallet, R., Ternacle, J., Damy, T., Guendouz, S., Bremont, C., Seemann, A., Gueret, P., Dubois-Rande, J.L. & Lim, P. 2014. Hemodynamic effects of Ivabradine in addition to dobutamine in patients with severe systolic dysfunction. *Int J Cardiol* **176**, 450–455.

Harjola, V.P., Lassus, J., Sionis, A., Kober, L., Tarvasmaki, T., Spinar, J., Parissis, J., Banaszewski, M., Silva-Cardoso, J., Carubelli, V. *et al.* 2015. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* **17**, 501–509.

Lattuca, B. & Roubille, F. 2015. Ivabradine: a promising drug in cardiogenic shock to prevent the undesirable sinus tachycardia induced by dobutamine? *Int J Cardiol* **178**, 308–310.

O'Connor, C.M., Gattis, W.A., Uretsky, B.F., Adams, K.F. Jr, McNulty, S.E., Grossman, S.H., McKenna, W.J., Zannad, F., Swedberg, K., Gheorghiade, M. & Califf, R.M. 1999. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* **138**, 78–86.

Ponikowski, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G., Coats, A.J., Falk, V., Gonzalez-Juanatey, J.R., Harjola, V.P., Jankowska, E.A. *et al.* 2016. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. In press.

Roubille, F. & Tardif, J.C. 2013. New therapeutic targets in cardiology: heart failure and arrhythmia: HCN channels. *Circulation* **127**, 1986–1996.

Roubille, F., Lattuca, B., Busseuil, D., Leclercq, F., Davy, J.M., Rheaume, E. & Tardif, J.C. 2013. Is ivabradine suitable to control undesirable tachycardia induced by dobutamine in cardiogenic shock treatment? *Med Hypotheses* **81**, 202–206.

Thiele, H., Zeymer, U., Neumann, F.J., Ferenc, M., Olbrich, H.G., Hausleiter, J., Richardt, G., Hennersdorf, M., Empen, K., Fuernau, G. *et al.* 2012. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* **367**, 1287–1296.

Thiele, H., Zeymer, U., Neumann, F.J., Ferenc, M., Olbrich, H.G., Hausleiter, J., de Waha, A., Richardt, G., Hennersdorf, M., Empen, K. *et al.* 2013. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* **382**, 1638–1645.

Wang, X.C., Zhu, D.M. & Shan, Y.X. 2015. Dobutamine therapy is associated with worse clinical outcomes compared with nesiritide therapy for acute decompensated heart failure: a systematic review and meta-analysis. *Am J Cardiovasc Drugs* **15**, 429–437.