

# Acute-phase administration of ivabradine supported by intra-aortic balloon pump induces myocardial recovery without significant haemodynamic worsening in a patient with acute fulminant myocarditis: a case report

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## Background

Ivabradine can reduce the heart rate without affecting myocardial contractility or vascular tone. Current guidelines recommend its use for treating patients with chronic heart failure who have a high heart rate ( $\geq 75$  b.p.m.) and persistent symptoms despite guideline-directed therapy. Nonetheless, little is known about its efficacy in patients with acute cardiogenic shock. We report a case of successful treatment of cardiogenic shock.

## Case summary

A 53-year-old previously healthy man was admitted due to cardiogenic shock with acute fulminant myocarditis. The patient was placed on intra-aortic balloon pump support and was given guideline-directed therapy including inotropic agents and furosemide. However, no improvement was seen in haemodynamics and the patient was in sinus tachycardia (116 b.p.m.). On Day 2, ivabradine therapy was initiated to reduce the myocardial workload and stabilize the haemodynamic parameters. As heart rate decreased, his symptoms improved and urine output increased without affecting the blood pressure. Subsequently, the patient recovered from cardiogenic shock. The intra-aortic balloon pumping was discontinued on Day 7, and the patient was discharged on Day 22.

## Discussion

Ivabradine has the potential to induce rapid cardiac recovery and haemodynamic improvement in the acute phase of heart failure if supported by intra-aortic balloon pump.

## Keywords

Case report • Cardiogenic shock • Fulminant myocarditis • Intra-aortic balloon pump • Ivabradine

## ESC curriculum

6.4 Acute heart failure • 7.1 Haemodynamic instability

## Learning points

- If used under the support of intra-aortic balloon pump, ivabradine can lead to haemodynamic recovery from acute cardiogenic shock.
- 'Supported ivabradine' in the acute phase of heart failure may be a novel indication of the drug in addition to the guideline-recommended use for chronic heart failure.

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## Introduction

Ivabradine is a specific blocker of the  $I_f$  'funny' current mediated by hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 and is used to regulate sinus node activity. Ivabradine can reduce the heart rate (HR) without affecting myocardial contractility or vascular tone.<sup>1</sup> Guidelines recommend its use as a treatment for patients with chronic heart failure who have a high HR ( $\geq 75$  b.p.m.) and persistent symptoms despite guideline-recommended therapy. However, little is known about its efficacy in patients with cardiogenic shock and acute heart failure.<sup>2</sup> In a damaged heart, an appropriate HR reduction can induce rapid myocardial recovery because HR is a major determinant of myocardial oxygen consumption. Thus, in terms of haemodynamics, the ivabradine administration is safe in normal cardiac function. However, in depressed left-ventricular function, a slight decrease of cardiac output (CO) secondary to HR reduction may worsen the heart failure. Thereby, the ivabradine administration tends to exacerbate haemodynamics.

## Time Line

Time	Events
18 October 2020	A 59-year-old male with dyspnoea was admitted to our hospital and transferred to the intensive care unit (ICU) due to cardiogenic shock. An intra-aortic balloon pump (IABP) and Swan–Ganz catheter were inserted. Administration of inotropic agents and furosemide was started.
20 October 2020	Administration of ivabradine was started.
24 October 2020	The IABP was removed because patient's symptoms and parameters improved.
2 November 2020	Discharged from ICU without inotropic agents and furosemide.
5 November 2020	Ivabradine was replaced by a beta-blocker (bisoprolol).
6 November 2020	The patient was discharged on Day 22 of hospitalization.

Herein, we report a case of fulminant myocarditis with acute cardiogenic shock in which ivabradine successfully induced haemodynamic recovery under IABP support.

## Case presentation

A 53-year-old man without past illness was brought to the emergency department complaining of shortness of breathing. Two days before admission, he had a high fever and dry cough. He showed a cold sweat and bilateral lower pedal oedema. On auscultation, wheezing was heard in all lung fields, and the third and fourth heart sounds were audible. His vital parameters were as follows: HR, 149/min (sinus tachycardia), blood pressure (BP), 98/48 mmHg, and peripheral oxygen saturation ( $SpO_2$ ), 84% on 10 L oxygen. He received non-invasive positive-pressure ventilation (continuous positive airway pressure 6  $cmH_2O$ ; fraction of inspired oxygen, 60%), after which his  $SpO_2$  improved to 100%.

Chest X-ray revealed cardiomegaly (cardiothoracic ratio, 56%) and pulmonary congestion (Figure 1A). Electrocardiography revealed sinus

tachycardia and non-specific bundle branch block with secondary ST-segment changes (Figure 1B). Echocardiogram showed diffuse myocardial oedema and hypokinesia left-ventricular ejection fraction (LVEF) of 20%. The results of the blood test performed on admission are presented in Table 1. An elevated lactate level, acidosis, and a low oxygen level were observed on arterial blood gas analysis. The white blood cell count (15 180/ $\mu L$ ) and levels of C-reactive protein (3.00 mg/dL), lactate dehydrogenase, creatine kinase, creatine kinase-MB, and troponin I levels were elevated. Additionally, the brain natriuretic peptide (BNP) level was 316.0 pg/mL, indicating positive inflammation and acute myocardial injury and congestion. Emergent coronary angiography revealed no significant stenosis. Since acute myocarditis was highly suspected, we performed a right-sided endomyocardial biopsy, the results of which confirmed the diagnosis of lymphocytic myocarditis 3 days later (Figure 1C). The patient was placed on IABP support and transferred to the ICU.

The patient's clinical course and management during admission at the ICU are shown in Figure 2. We immediately initiated guideline-directed medical therapies. The patient received carperitide (0.02  $\mu g/kg/min$ ), milrinone (0.33  $\mu g/kg/min$ ), dobutamine (2.5  $\mu g/kg/min$ ), and furosemide (2.5 mg/h); nonetheless, he showed no improvement in symptoms, LVEF, or urine output. He had a high HR (131/min), low BP (92/52 mmHg), low cardiac index (1.7/min/ $m^2$ ), and low urine output (100 mL/h) on Day 2. Echocardiography revealed an LVEF of 23.6%, inferior vena cava diameter of 23.8 mm without respiratory fluctuation (Supplementary material online, Figure S1).

We introduced the administration of ivabradine (Coralan® 2.5 mg twice daily) on Day 2 because we suspected his high HR was responsible for his unchanged condition. The results of Swan–Ganz catheterization for the first 48 h after the initiation of ivabradine are shown in Table 2. After 12 h of administration of ivabradine, his vital parameters were as follows: HR, 115/min, BP 91/53 mmHg, cardiac index (CI) 2.5/min/ $m^2$ , urine output, 150 mL/h. After 24 h of administration of ivabradine, his symptoms improved, and parameters are as follows: HR, 103/min, BP, 96/49 mmHg, CI 2.6/min/ $m^2$ ; BNP, 482 pg/mL; urine output, 180 mL/h. Concurrently, pulmonary arterial pressure improved due to increased urine output and CI improvement. The required dose of inotropic agents and furosemide decreased. On Day 6, the IABP was removed. On Day 19, ivabradine was replaced by a beta-blocker (bisoprolol 0.625 mg once daily) because the patient's condition was stable even without IABP support or inotropic agents. On Day 20, chest X-ray revealed no cardiomegaly (cardiothoracic ratio, 43%) and no abnormality except that the costo-phrenic angle was slightly opaque (Supplementary material online, Figure S2A). Electrocardiography revealed sinus rhythm (HR, 52/min) and no specific abnormality (Supplementary material online, Figure S2B). Echocardiogram revealed a LVEF of 42.5% and inferior vena cava diameter of 13.2 mm with respiratory fluctuation (Supplementary material online, Figure S1B).

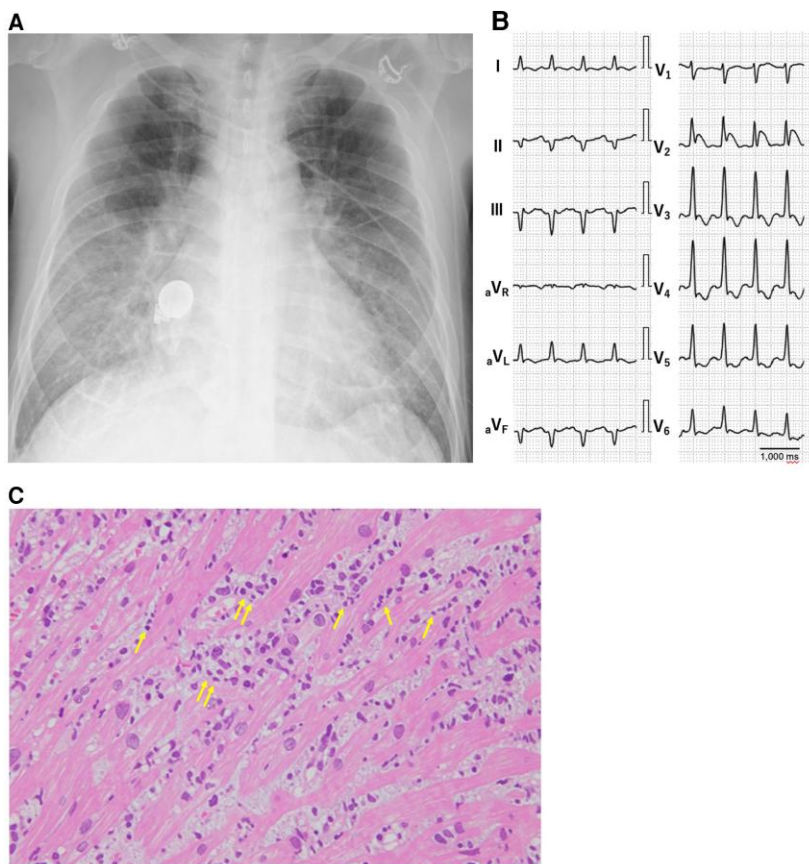
The patient was discharged on Day 22.

He had no symptoms and his general condition was good after 3 weeks post discharge. He has not been hospitalized since discharge.

## Discussion

In acute heart failure, tachycardia is the compensatory reaction to preserve haemodynamics. However, a higher HR in depressed LV function leads to incomplete relaxation of the left ventricle and an inappropriate increase of myocardial oxygen consumption.<sup>1</sup> Thus, tachycardia in acute heart failure often worsens LV function and haemodynamics.

Beta-blockers have been conventionally used to decrease HR and improve symptoms in patients with chronic heart failure. However, due to the negative inotropic effect of beta-blockers, the physician sometimes



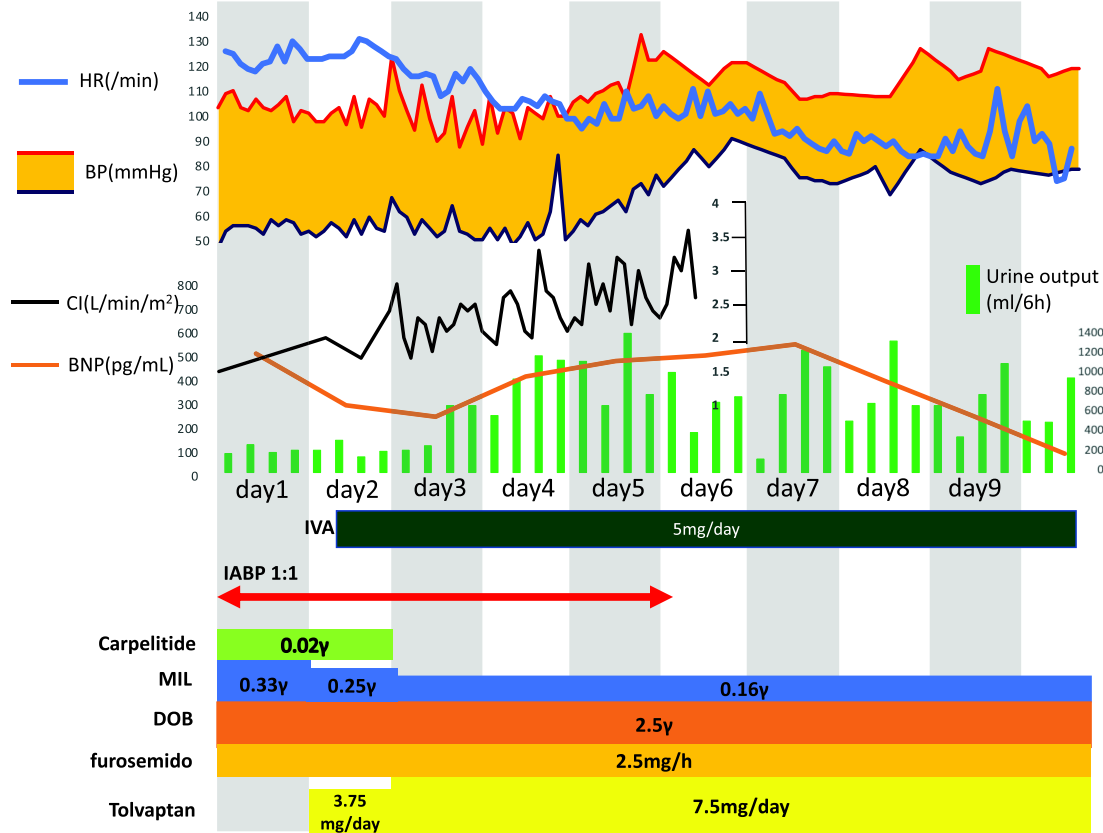
**Figure 1** Chest X-ray (A), 12-lead electrocardiography (B), and histopathology (C) on Day 1. Histopathology of the right-ventricular endomyocardial specimen taken on admission (haematoxylin and eosin staining  $\times 400$ ). Marked and diffused infiltration of lymphocytes (arrow) within the myocardium is observed, while eosinophilic infiltration is absent. The findings are consistent with acute lymphocytic myocarditis.

**Table 1** Laboratory data on admission

WBC	15180/ $\mu$ L	AST	85 IU/L	LDH	503 IU/L
Neu	65.9%	ALT	37 IU/L	CK	481 IU/L
Ly	21.3%	BUN	19.1 mg/dL	CK-MB	48 IU/L
Eosino	0.7%	Cre	0.94 mg/dL	BNP	316.0 pg/mL
RBC	$567 \times 10^4$ / $\mu$ L	Na	135 mEq/L	Troponin I	8.573 ng/mL
Hb	17.1 g/dL	K	4.5 mEq/L		
Ht	50.0%	Cl	98 mEq/L	FiO <sub>2</sub>	100.0%
Plt	$15.3 \times 10^4$ / $\mu$ L	CRP	3.00 mg/dL	pH	7.320
				PaCO <sub>2</sub>	39.8 mmHg
PT	11.0 s	Free T3	2.06 pg/mL	PaO <sub>2</sub>	64.3 mmHg
PT-INR	0.95	Free T4	0.87 ng/dL	HCO <sub>3</sub> <sup>-</sup>	20.5 mmol/L
APTT	27.4 s	TSH	0.806 $\mu$ IU/L	Lactate	32.00 mg/dL
APTT %	103%				
D-Dimer	2.9 $\mu$ g/mL				

Reference values: WBC, 3500–9900/ $\mu$ L; Neu, 38–75%; Ly, 17–49%; Eosino, 0–8%; RBC,  $395\text{--}540 \times 10^4$ / $\mu$ L; Hb, 12.7–16.4 g/dL; Ht, 37.8–48.2%; Plt,  $12\text{--}40 \times 10^4$ / $\mu$ L; AST, 5–40 IU/L; ALT, 37 IU/L; BUN, 8.0–23.0 mg/dL; Cre, 0.62–1.10 mg/dL; Na, 136–148 mEq/L; K, 3.6–5.0 mEq/L; CRP, <0.25 mg/dL; LDH, 130–250 IU/L; CK, 35–200 mg/dL; CK-MB, 5–22 IU/L; BNP, <18.4 pg/mL; troponin I, <0.025 ng/mL; PT, 10.5–13.5 s; PT-INR, 0.85–1.15; APTT, 24–39 s; APTT%, 60–140%; D-dimer, 0.0–0.9  $\mu$ g/mL; free T3, 2.3–4.1 pg/mL; free T4, 0.88–1.50 ng/dL; TSH, 0.806  $\mu$ IU/mL; pH, 7.36–7.44; PaCO<sub>2</sub>, 36.0–44.0 mmHg; PaO<sub>2</sub>, 85.0–95.0 mmHg; HCO<sub>3</sub><sup>-</sup>, 20.0–26.0 mmol/L; lactate, 4.5–14.4 mg/dL.

WBC, white blood cells; Neu, neutrophils; Ly, lymphocytes; Eosino, eosinophils; RBC, red blood cells; Hb, haemoglobin; Ht, haematocrit; Plt, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; CRP, C-reactive protein; LDH, lactate dehydrogenase; CK, creatine phosphokinase; CK-MB, creatine phosphokinase-muscle brain; BNP, brain natriuretic peptide; TSH, thyroid-stimulating hormone.



**Figure 2** Changes in haemodynamics and the treatment. Ivabradine was initiated on Day 2 because guideline-directed medications combined with intra-aortic balloon pump did not improve haemodynamic parameters and the sinus tachycardia continued. 'Supported ivabradine' induced favourable changes in the parameters. HR, heart rate; BP, blood pressure; BNP, brain natriuretic peptide; CI, cardiac index; IVA, ivabradine; IABP, intra-aortic balloon pump; hANP, human atrial natriuretic peptide; MIL, milrinone; DOB, dobutamine.

**Table 2** The change of vital sign and Swan–Ganz data before and after prescription of ivabradine

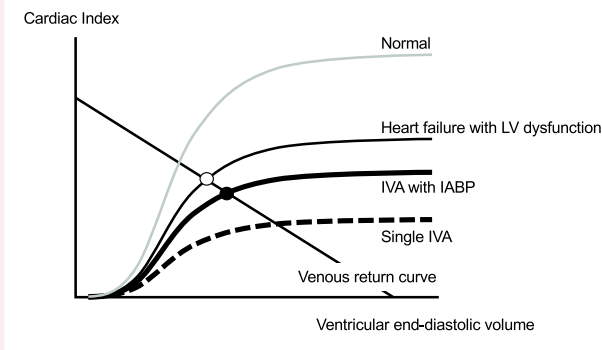
	Before ivabradine	After 12 h	After 24 h	After 36 h	After 48 h
sBP (mmHg)	94	91	96	95	104
dBP (mmHg)	55	53	49	51	61
sPAP (mmHg)	33	25	28	23	24
dPAP (mmHg)	22	20	18	13	14
HR (/min)	112	115	103	99	97
CCO (L/min)	3.4	4.3	4.4	4.5	5.2
CCI (L/min/m <sup>2</sup> )	2	2.5	2.6	2.7	3.1
SvO <sub>2</sub> (%)	74	72	75	80	77
CVP (mmHg)	15	22	16	11	9
BNP (pg/mL)	419		482		506

Reference values: sBP, 90–140 mmHg; dBP, 50–90 mmHg; sPAP, 15–30 mmHg; dPAP, 4–18 mmHg; HR, 60–100/min; CCO, 4–8 L/min; CCI, 2.6–4.2 L/min/m<sup>2</sup>; SvO<sub>2</sub>, 70–80%; CVP, 5–10 mmHg; BNP, <18.4 pg/mL.

sBP, systolic blood pressure; dBP, diastolic blood pressure; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; HR, heart rate; CCO, continuous cardiac output; CCI, continuous cardiac index; SvO<sub>2</sub>, mixed venous oxygen saturation; CVP, central venous pressure; BNP, brain natriuretic peptide.

hesitates to increase the dose to the target HR level, especially in acute heart failure with LV dysfunction. The specific effect of Ivabradine on the *I<sub>f</sub>* 'funny' current does not directly affect myocardial contractility and vascular characteristics.<sup>3</sup> Animal studies have shown that using

ivabradine for treating acute heart failure results in increased CO and decreased LV end-diastolic pressure (LVEDP).<sup>4</sup> However, another animal study found that ivabradine decreased CO and HR and increased central venous pressure and stroke volume.<sup>5</sup> Those data indicated



**Figure 3** The illustration of changes of the cardiac output curve under 'supported ivabradine'. The circulatory equilibrium framework consists of the cardiac output curve, representing ventricular pumping ability, and venous return. The patient in acute heart failure with left-ventricular dysfunction has a lower cardiac output curve than normal (thin line). The heart rate is a major determinant of the slope in cardiac output curve. The bradycardia by ivabradine might decrease cardiac output curve further (dashed line). Intra-aortic balloon pump support preserved the decrease of cardiac output curve within acceptable haemodynamic level (bold line). LV, left ventricle; IVA, ivabradine; IABP, intra-aortic balloon pump.

that the pure bradycardic effect of ivabradine has a bidirectional possibility to improve and worsen haemodynamics in acute heart failure. However, the ESC guideline does not support the use of ivabradine for acute heart failure.

At the time of presentation to the hospital, the patient showed a decompensated cardiogenic shock with sinus tachycardia. To reduce HR, we used ivabradine under IABP support. Although BP was preserved after ivabradine administration, the BNP level increased, which indicated an increase in LVEDP. In this situation, we can explain the haemodynamics by illustrating the circulatory equilibrium, which consists of the CO curve, representing ventricular pumping ability, and venous return. As shown in [Figure 3](#), the HR reduction by ivabradine in this patient might have decreased CO curve from thin line to dashed line. Meanwhile, IABP support preserved the attenuation and shift the curve from dashed to bold line. As a result of preservation of the CO curve by IABP, the haemodynamic deterioration by ivabradine was limited to an acceptable level. Navaratnarajah *et al.*<sup>6</sup> showed that the combination of ivabradine and LV assist device significantly improves cardiac energetics and induces reverse remodelling in a rat model with myocardial infarction-induced heart failure. Our concept is in line with their findings. IABP support prevented the worsening of haemodynamics by ivabradine-induced bradycardia and exerted mechano-chronotropic LV unloading in this patient.

## Conclusion

In conclusion, ivabradine has the potential to induce rapid cardiac recovery by chronotropic LV unloading. The combination of IABP with ivabradine prevented the haemodynamic worsening and augmented the LV unloading effect by its systolic unloading effect. The concept of 'supported ivabradine' may be a good option for treating acute heart failure with sinus tachycardia. Further large-scale studies are required to address the optimization of this strategy.

This study has a limitation. There was insufficient echocardiography data such as those related to left ventricular outflow tract velocity time integral (LVOT-VTI) and trans-mitral flow because the aforementioned parameters are not routinely measured in our institution.

## Lead author biography



Dr Moriyasu Ando graduated from Gifu university graduate school of medicine, Gifu, Japan in 2020. He is a resident of internal medicine at Ogaki Municipal Hospital, Ogaki, Japan, and is actively involved in heart failure treatment.

## Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for the submission and publication of this case report, including the images and associated text, has been obtained from the patient in line with the COPE guidelines.

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## References

- Selby DE, Palmer BM, LeWinter MM, Meyer M. Tachycardia-induced diastolic dysfunction and resting tone in myocardium from patients with a normal ejection fraction. *J Am Coll Cardiol* 2011;**58**:147–154.
- Pascual Izco M, Alonso Salinas GL, Sanmartín Fernández M, Del Castillo Carnevali H, Jiménez Mena M, Camino López A, Zamorano Gómez JL. Clinical experience with ivabradine in acute heart failure. *Cardiology* 2016;**134**:372–374.
- Seo Y, Ohte N. Effects of heart rate reduction by ivabradine for heart failure beyond  $\beta$ -blockers. *Circ J* 2019;**83**:1991–1993.
- Peschanski N, Harouki N, Soulie M, Lachaux M, Nicol L, Remy-Jouet I, Henry JP, Dumesnil A, Renet S, Fougerousse F, Brakenhielm E, Ouvrard-Pascaud A, Thuillez C, Richard V, Roussel J, Mulder P. Transient heart rate reduction improves acute decompensated heart failure-induced left ventricular and coronary dysfunction. *ESC Heart Fail* 2021;**8**:1085–1095.
- Pascual Izco M, Ramírez-Carracedo R, Hernández Navarro I, Osorio Ruiz Á, Castejón Navarro B, Cuadrado Berrocal I, Largo Aramburu C, Alonso Salinas GL, Díez J, Saura Redondo M, Zamorano JL, Zaragoza C, Sanmartín M. Ivabradine in acute heart failure: effects on heart rate and hemodynamic parameters in a randomized and controlled swine trial. *Cardiol J* 2020;**27**:62–71.
- Navaratnarajah M, Ibrahim M, Siedlecka U, van Doorn C, Shah A, Gandhi A, Dias P, Sarathchandra P, Yacoub MH, Terracciano CM. Influence of ivabradine on reverse remodelling during mechanical unloading. *Cardiovasc Res* 2013;**97**:230–239.