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Landiolol for managing atrial fibrillation in intensive care

Sebastian Rehberg[1]*, Michael Joannidis[2], Tony Whitehouse[3], and Andrea Morelli[4]

[1]*Department of Anaesthesiology, University Hospital of Greifswald, 17475 Greifswald, Germany*
[2]*Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, A-6020 Innsbruck, Austria*
[3]*Department of Critical Care and Anaesthesia, University Hospital Birmingham, Edgbaston, B15 2GW Birmingham, UK*
[4]*Department of Anesthesiology and Intensive Care Medicine, University of Rome "La Sapienza", Italy Policlinico Umberto I° Hospital, Viale del Policlinico 155, 00161 Rome, Italy*

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Landiolol is an injectable ultrashort acting beta-blocker with high beta1 selectivity indicated for heart rate control of atrial fibrillation in the emergency and critical care setting. Accordingly, landiolol is associated with a significantly reduced risk of arterial hypotension and negative inotropic effects. Based on this particular profile along with the clinical experience in Japan for more than a decade landiolol represents a promising agent for the management of elevated heart rate and atrial fibrillation in intensive care patients even with catecholamine requirements. This article provides a review and perspective of landiolol for heart rate control in intensive care patients based on the current literature.

Atrial fibrillation (Afib) is a common complication in intensive care units (ICU) and associated with increased mortality rates as well as prolonged ICU and hospital length of stay.[1-3] The incidence of Afib in critically ill patients managed in mixed ICUs can be as high as 30% with new-onset Afib usually ranging between 4.5% and 15%.[1,2] Notably, patients with sepsis are particularly prone to develop Afib with recent data providing incidences of new-onset Afib even ranging from 23% to 40%.[4-10]

Risk factors for developing Afib during ICU stay include age older than 65 years, arterial hypertension, left atrial dilatation and diastolic dysfunction, systemic inflammatory response syndrome, and sepsis. In addition, hypovolaemia, electrolyte disorders, increased serum C-reactive protein levels, and vasopressor treatment are common risk factors observed in intensive care patients.[1,11]

Short-term complications include an increased risk of weaning failure in mechanically ventilated patients.[12] For septic patients developing new-onset Afib during ICU stay, long-term complications such as a greater 5 years of risk of hospitalization for heart failure[13] and increased mortality rates[14] have been described.

Current guidelines for the treatment of Afib recommend to first identify and treat the cause, such as correcting hypovolaemia or electrolyte imbalances, before initiating any medical treatment with antiarrhythmic drugs. If medical heart rate control is required, intensivists can rely on similar compounds as used for the treatment of post-operative Afib.

Of note, guidelines for the treatment of Afib have been recently updated.[15] While administration of beta-blockers or calcium blockers is recommended with due diligence in patients with hypotension or heart failure, digitalis or amiodarone were recommended in patients with Afib and concomitant heart failure or in the setting of hypotension. Notably, the new guidelines propose a distinct algorithm for heart rate control depending on the left ventricular ejection function (LVEF) of the patient: If LVEF is >40%, calcium channel blockers or beta-blockers may be initiated for heart

*Corresponding author. Tel: +49 (0)3834 865801, Fax: +49 (0)3834 865802, Email: Sebastian.Rehberg@uni-greifswald.de

rate control. In case of a compromised left ventricular ejection function (LVEF < 40%); however, clinicians may initiate beta-blockers at the lowest possible dose to achieve heart rate control. Amiodarone is currently reserved only if cardiac function is severely depressed (LVEF < 25%).[15]

Intensive care unit patients frequently suffer from cardiac dysfunction. Due to their long half-life and potential hypotensive effects, beta-blockers may be difficult to dose and to titrate in these patients. Landiolol is a new highly beta1 selective ultra-short acting beta-blocker (β1/β2 selectivity = 255:1 and a half-life of 4 min) with minimal negative inotropic and hypotensive effects. It has been available in Europe for 1 year, but has already been used successfully in intensive care in Japan for over 10 years.[16-20] The Japanese Circulation Society recommends landiolol, along with carvedilol or bisoprolol, as first line treatment (Class I-B) for heart rate control of Afib in the absence of an accessory pathway for patients with heart failure.[20] Landiolol has also been used safely for Afib in patients with cardiac dysfunction.[21-25]

The following studies describe the successful use of landiolol in different patient cohorts and with different therapeutic regimes. Yoshida *et al.*[16] reported successful heart rate control with landiolol in 80 ICU patients. Landiolol was used primarily for Afib and arrhythmia (68%) in medical patients and for heart rate control to prevent ischaemia (71%) in post-operative patients. Landiolol significantly reduced heart rate from 105 ± 23 b.p.m. to 83 ± 8 b.p.m. ($P < 0.001$) without impairing arterial blood pressure. Decreases in heart rate were similar in patients under catecholamine treatment (102 ± 23 b.p.m. decreased to 84 ± 9 b.p.m.) and in patients without catecholamine treatment (114 ± 20 b.p.m. decreased to 85 ± 7 b.p.m.). Notably, 47% of post-surgical patients and 50% of medical intensive care patients converted to sinus rhythm during treatment with landiolol. The authors used a titrated, continuous infusion with a median dose of 5 mcg/kg/min over 2 days without any loading doses. During landiolol therapy, no adverse effects such as severe left ventricular dysfunction, severe hypotension, severe bradycardia, bronchospasm, deterioration of diabetes mellitus, or deteriorating peripheral vascular disease were reported. In one-third of the patients, transition to chronic oral beta-blocker treatment was required and achieved without complications such as rebound tachycardia.

Sasaki *et al.*[17] retrospectively studied 95 critical ill patients from a multidisciplinary ICU, who were treated with low-dose landiolol (mean 3.2 ± 1.9 mcg/kg/min) for an average duration of 41 ± 50 h. Heart rate was significantly decreased within 1 h and still sustained after 6 h. There was minimal impact on arterial blood pressure (less than 10% decrease) and 26 patients (51%) converted to sinus rhythm within 227 ± 399 min.

In addition to heart rate control for Afib, landiolol has been used as complement to analgosedation to reduce the risk of ischaemia[17] due to short-term haemodynamic stress caused by interventions in ICU patients such as intubation or bronchoscopy.[18] However, this indication should be considered with extreme caution only after careful exclusion of any compensatory cause for sinus tachycardia such as bleeding, anaemia, pain, anxiety, fever, and other factors influencing haemodynamic changes. Furthermore, close haemodynamic monitoring is mandatory during intravenous beta-blocker administration.[19]

A particular cohort of patients who benefit from heart rate control with landiolol is septic patients developing Afib.[20,26-28] Of note, this indication is different from the currently discussed heart rate control in septic shock patients with sinus tachycardia despite fluid resuscitation as originally described by Morelli and colleagues. Okajima *et al.*[20] retrospectively compared severe sepsis patients treated with landiolol vs. patients receiving standard of care (calcium blockers, disopyramid, or amiodarone). Baseline characteristics were mostly comparable between study groups (e.g. age, underlying disease, organ dysfunction status, and severity). Notably, heart rate was higher and systolic arterial pressure was lower in the landiolol group at baseline. After 1 h treatment with a continuous infusion of 6.1 ± 4.7 mcg/kg/min, landiolol was able to significantly reduce HR from 145 ± 14 to 119 ± 28 b.p.m. without reducing arterial pressure. In addition, heart rate was better controlled in landiolol vs. standard of care, and the conversion to sinus rhythm already occurred in 10/39 patients after 1 h. Conversion rate increased to 55% after 8 h and reached 70% after 24 h, whereas it was only 18% and 34%, respectively, for standard of care at these time points. Heart rate was continuously decreased and well controlled over 24 h, with doses slightly decreasing from 5.5 ± 4.1 mcg/kg/min at 8 h to 4.2 ± 4.3 mcg/kg/min at 24 h. The total infusion duration was 80.7 ± 78.5 h. Neither a relevant change of arterial blood pressure nor significant bradycardia were observed during the treatment period.

These findings are consistent with the results of another Japanese team[26] who treated 29 septic patients with landiolol infusion for 48 h. Except lower severity scores (APACHE-II score of 19 ± 7 vs. 22.8 ± 5.4) the patients were comparable to the ones of the formerly discussed study. Heart rate was decreased from 125 ± 22 to 92 ± 12 b.p.m. within 12 h and maintained below 100 b.p.m. for the next 36 h. Heart rate control (<95 b.p.m.) was achieved in 69% of patients within 12 h and most of arrhythmia disorders were no longer present at this time point (73% of Afib and 100% ventricular tachycardia disappeared).

The initial infusion dose was on average 4.1 ± 3.1 mcg/kg/min and continued at 3.7 ± 2.5 mcg/kg/min for 24 h, to be slightly decreased to 3.3 ± 2.6 mcg/kg/min at 48 h to maintain heart rate target below 95 b.p.m. while avoiding systolic blood pressure to drop below 90 mmHg. In addition, heart rate was controlled without significant effects on mean arterial blood pressure, central venous pressure, oxygen saturation (SpO2), and PaO2/FiO2 (arterial oxygen partial pressure to fractional inspired oxygen ratio). Of note, a decrease in systolic blood pressure (<90 mmHg) was observed in some patients during landiolol treatment (0.28 events per person-day). However, only few cases were attributed to landiolol. No bradycardias were recorded.

In summary, these studies suggest that low dose landiolol (<10 mcg/kg/min) is able to safely control heart rate with minimal impact on blood pressure and cardiac index in patients with severe sepsis developing new-onset Afib. The relevance of this finding is emphasized by a large retrospective cohort study[29] that compared the four classes of therapeutic agents. It recommended beta-blocker,

calcium-blocker, digoxin, and amiodarone for heart rate control. In septic patients, beta-blockers were associated with a better outcome, even after matching sub-groups using propensity score analyses.[29]

The current literature not only supports the necessity to reintroduce chronic beta-blocker in ICU patients before discharge but also to restart beta-blocker medication much earlier during ICU stay or even to continue it during critical illness.[30,31] Administrating a negatively inotropic drug in haemodynamically impaired patients with sepsis-induced myocardial dysfunction is a challenge as it risks a fall in cardiac output and arterial blood pressure. Longer-acting beta-blockers are considered difficult to manipulate and for patients treated with vasopressors needing heart rate control, beta-blockade is often not used. However, a recent retrospective analysis in patients with severe sepsis or septic shock found that discontinuing chronic beta-blocker medication during the acute phase (2 days before until 3 days after diagnosis of sepsis) was associated with worse outcome. In addition, continuing pre-existing beta-blocker therapy was an independent predictor of improved survival.[30]

Notably, our team[32]and others[33] have demonstrated that beta-blockers can be combined with norepinephrine without clinical relevant negative impact on cardiac output or haemodynamics, if patients are selected carefully and beta-blocker therapy can be closely titrated.[34,32] Accordingly, the short-acting beta-blocker landiolol represents a welcome option for controlling heart rate in severe sepsis patients with Afib.

A different indication for heart rate control in septic shock patients is currently under investigation.[35,36] There is increasing evidence that in fluid resuscitated patients with persisting sinus tachycardia, beta-blocker treatment attenuates myocardial dysfunction by optimizing cardiac filling and arterial-heart coupling,[37] reducing catecholamine requirements, and subsequent catecholamine induced cardiac apoptosis[38] as well as reducing inflammation and restoring vascular reactivity.[39,40]

Landiolol has been shown to share similar benefits as esmolol in animal model of sepsis, by modulating inflammation and improving survival. Hagiwara *et al*. demonstrated that animals treated with landiolol expressed lower levels of High-mobility group box 1, a key mediator of systemic inflammation, both in plasma and lung. In addition, landiolol was associated with significantly lower disease severity scores, less lung histopathology injuries, and lower cardiac dysfunction.[41]

The potential protective effect of landiolol has been confirmed in different models of sepsis, using 3 h of LPS (lipopolysaccharides) infusion and exploring other organ dysfunction: When infused along with LPS, landiolol decreased or even normalized markers of inflammation such as tumour necrosis factor alpha (TNF-α) and endothelin-1, in the heart,[42] the kidney,[43] and the liver.[44] Furthermore, markers of renal (neutrophil gelatinase-associated lipocalin and blood urea nitrogen)[43] and liver dysfunction (alanine aminotransferase and aspartate aminotransferase) were reduced.[44]

Using the same model of LPS infusion over 3 h, another team was able to show that landiolol attenuated and sometimes even prevented acute lung injury by normalizing the altered levels of pulmonary endothelin-1 and endothelin-A receptors. In addition, landiolol induced significant down-regulation of endothelin-B receptors in lung tissues. However, no effect was observed on inflammatory mediators such as TNF-α or interleukin-6 in both plasma and lung tissues.[45]

In conclusion, due to its high beta-1 selectivity with an ultra-short half-life and minimal impact on arterial blood pressure landiolol has a very promising pharmacologic profile for the use in critical ill patients, even if they require haemodynamic support. Landiolol has been used safely for heart rate control in ICU patients with new onset-Afib including severe sepsis in Japan. Notably, landiolol therapy resulted in a conversion to sinus rhythm in 50–75% of the patients. These promising results require verification in populations outside of Japan. In addition, potential benefits of landiolol such as attenuation of inflammation and improving outcomes in septic shock patients without Afib need to be confirmed in future trials.

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References

1. Yoshida T, Fujii T, Uchino S, Takinami M. Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. *J Intensive Care* 2015;**3**:19.
2. Moss TJ, Calland JF, Enfield KB, Gomez-Manjarres DC, Ruminski C, DiMarco JP, Lake DE, Moorman JR. New-onset atrial fibrillation in the critically ill. *Crit Care Med* 2017;**45**:790–797.
3. Shaver CM, Chen W, Janz DR, May AK, Darbar D, Bernard GR, Bastarache JA, Ware LB. Atrial fibrillation is an independent predictor of mortality in critically ill patients. *Crit Care Med* 2015;**43**:2104–2111.
4. Liu WC, Lin WY, Lin CS, Huang HB, Lin TC, Cheng SM, Yang SP, Lin JC, Lin WS. Prognostic impact of restored sinus rhythm in patients with sepsis and new-onset atrial fibrillation. *Crit Care* 2016;**20**:373.
5. Lewis O, Ngwa J, Gillum RF, Thomas A, Davis W, Poddar V, Adams GR, Thomas AJ, Mehari A. Incidence, risk factors and outcomes of new onset supraventricular arrhythmias in african american patients with severe sepsis. *Ethn Dis* 2016;**26**:205–212.
6. Klein Klouwenberg PM, Frencken JF, Kuipers S, Ong DS, Peelen LM, van Vught LA, Schultz MJ, van der Poll T, Bonten MJ, Cremer OL; MARS Consortium. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis. A cohort study. *Am J Respir Crit Care Med* 2017;**195**:205–211.
7. Kuipers S, Klein Klouwenberg PM, Cremer OL. Incidence, risk factors and outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review. *Crit Care* 2014;**18**:688.
8. Guenancia C, Binquet C, Laurent G, Vinault S, Bruyère R, Prin S, Pavon A, Charles P-E, Quenot J-P, Yende S. Incidence and predictors of new-onset atrial fibrillation in septic shock patients in a medical ICU: data from 7-day Holter ECG monitoring. *PLoS One* 2015;**10**:e0127168.
9. Koyfman L, Brotfain E, Kutz R, Frenkel A, Schwartz A, Boniel A, Zlotnik A, Klein M. Epidemiology of new-onset paroxysmal atrial fibrillation in the General Intensive Care Unit population and after discharge from ICU. A retrospective epidemiological study. *Anaesthesiol Intensive Ther* 2015;**47**:309–314.
10. Walkey AJ, Greiner MA, Heckbert SR, Jensen PN, Piccini JP, Sinner MF, Curtis LH, Benjamin EJ. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am Heart J* 2013;**165**:949–955.e3.

11. Makrygiannis SS, Margariti A, Rizikou D, Lampakis M, Vangelis S, Ampartzidou OS, Katsifa K, Tselioti P, Foussas SG, Prekates AA. Incidence and predictors of new-onset atrial fibrillation in noncardiac intensive care unit patients. *J Crit Care* 2014;**29**:697.e1–695.
12. Tseng YH, Ko HK, Tseng YC, Lin YH, Kou YR. Atrial fibrillation on intensive care unit admission independently increases the risk of weaning failure in nonheart failure mechanically ventilated patients in a medical intensive care unit: a retrospective case-control study. *Medicine (Baltimore)* 2016;**95**:e3744.
13. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest* 2014;**146**:1187–1195.
14. Gandhi S, Litt D, Narula N. New-onset atrial fibrillation in sepsis is associated with increased morbidity and mortality. *Neth Heart J* 2015;**23**:82–88.
15. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar A, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–1678.
16. Yoshida Y, Terajima K, Sato C, Akada S, Miyagi Y, Hongo T, Takeda S, Tanaka K, Sakamoto A. Clinical role and efficacy of landiolol in the intensive care unit. *J Anesth* 2008;**22**:64–69.
17. Sasaki H, Imaizumi H, Masuda Y, Tatsumi H, Goto K, Yoshida S, Ryan R, Asai Y. Clinical evaluation and prospects of landiolol in an intensive care unit ICU & CCU. *Jpn J Intensive Care Med* 2012;**36**: 671–676.
18. Hifumi T, Kato H, Koido Y, Kawakita K, Kuroda Y. Safety and effective use of landiolol in the ICU. *J Intensive Care* 2014;**2**:16.
19. Tochikubo J, Adachi YU, Ejima T, Numaguchi A, Matsuda N, Sato S, Shiiya N. Landiolol reduces hemodynamic responses to bronchoscopy-assisted suctioning in intubated ICU patients. *J Intensive Care* 2014; **2**:6.
20. Okajima M, Takamura M, Taniguchi T. Landiolol, an ultra-short-acting β1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. *World J Crit Care Med* 2015;**4**:251–257.
21. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). *Circ J* 2014;**78**:1997–2021.
22. Nitta D, Kinugawa K, Imamura T, Endo M, Amiya E, Inaba T, Maki H, Hatano M, Komuro I. An experience of landiolol use for an advanced heart failure patient with severe hypotension. *Int Heart J* 2015;**56**: 564–567.
23. Adachi T, Sato A, Baba M, Hiraya D, Hasegawa T, Kuroki K, Hoshi T, Aonuma K. Novel use of the ultra-short-acting intravenous β1-selective blocker landiolol for supraventricular tachyarrhythmias in patients with congestive heart failure. *Heart Vessels* 2014;**29**: 464–469.
24. Nagai R, Kinugawa K, Inoue H, Atarashi H, Seino Y, Yamashita T, Shimizu W, Aiba T, Kitakaze M, Sakamoto A, Ikeda T, Imai Y, Daimon T, Fujino K, Nagano T, Okamura T, Hori M; J-Land Investigators. Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short-acting β1-selective blocker landiolol with digoxin (J-Land Study). *Circ J* 2013;**77**:908–916.
25. von Haehling S, Bělohlávek J, Er F, Gassanov N, Guarracino F, Bouvet O. Landiolol for rate control management of atrial fibrillation in patients with cardiac dysfunction. *European Heart Journal Supplements* 2018;**20**(Suppl A):A19–A24.
26. Ueda TM, Yajima S, Misonoo Y, Suzuki T, Morisaki H. Landiolol therapy in septic patients: the feasibility study of the ultrashort acting beta1 adrenoreceptor blockade. *Intensive Care Med* 2010;**36**(Suppl 2):86–433.
27. Oka H, Sugimoto M, Azuma H. Efficacy of landiolol for the treatment of junctional ectopic tachycardia resulting from sepsis. *Cardiol Young* 2016;**26**:183–187.
28. Yoshida Y, Hongo T, Sakamoto A, Ogawa R. Successful management of tachycardiac atrial fibrillation in a septic patient with landiolol. *Anesth Analg* 2005;**100**:294.
29. Walkey AJ, Evans SR, Winter MR, Benjamin EJ. Practice patterns and outcomes of treatments for atrial fibrillation during sepsis: a propensity-matched cohort study. *Chest* 2016;**149**:74–83.
30. Fuchs C, Wauschkuhn S, Scheer C, Vollmer M, Meissner K, Kuhn SO, Hahnenkamp K, Morelli A, Gründling M, Rehberg S. Continuing chronic beta-blockade in the acute phase of severe sepsis and septic shock is associated with decreased mortality rates up to 90 days. *Br J Anaesth* 2017;**119**:1–10.
31. Noveanu M, Breidthardt T, Reichlin T, Gayat E, Potocki M, Pargger H, Heise A, Meissner J, Twerenbold R, Muravitskaya N, Mebazaa A, Mueller C. Effect of oral β-blocker on short and long-term mortality in patients with acute respiratory failure: results from the BASEL-II-ICU study. *Crit Care* 2010;**14**:R198.
32. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, Orecchioni A, D'Egidio A, D'Ippoliti F, Raffone C, Venditti M, Guarracino F, Girardis M, Tritapepe L, Pietropaoli P, Mebazaa A, Singer M. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA* 2013;**310**:1683–1691.
33. Balik M, Rulisek J, Leden P, Zakharchenko M, Otahal M, Bartakova H, Korinek J. Concomitant use of beta-1 adrenoreceptor blocker and norepinephrine in patients with septic shock. *Wien Klin Wochenschr* 2012;**124**:552–556.
34. Morelli A, Donati A, Ertmer C, Rehberg S, Kampmeier T, Orecchioni A, D'Egidio A, Cecchini V, Landoni G, Pietropaoli P, Westphal M, Venditti M, Mebazaa A, Singer M. Microvascular effects of heart rate control with esmolol in patients with septic shock: a pilot study. *Crit Care Med* 2013;**41**:2162–2168.
35. Pemberton P, Veenith T, Snelson C, Whitehouse T. Is it time to beta block the septic patient? *Biomed Res Int* 2015;**2015**:424308.
36. Rudiger A. Beta-block the septic heart. *Crit Care Med* 2010;**38**: S608–S612.
37. Morelli A, Singer M, Ranieri VM, D'Egidio A, Mascia L, Orecchioni A, Piscioneri F, Guarracino F, Greco E, Peruzzi M, Biondi-Zoccai G, Frati G, Romano SM. Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study. *Intensive Care Med* 2016;**42**:1528–1534.
38. Schmittinger CA, Dünser MW, Torgersen C, Luckner G, Lorenz I, Schmid S, Joannidis M, Moser P, Hasibeder WR, Halabi M, Steger CM. Histologic pathologies of the myocardium in septic shock: a prospective observational study. *Shock* 2013;**39**:329–335.
39. Kimmoun A, Louis H, Al Kattani N, Delemazure J, Dessales N, Wei C, Marie PY, Issa K, Levy B. β1-Adrenergic inhibition improves cardiac and vascular function in experimental septic shock. *Crit Care Med* 2015;**43**:e332–e340.
40. García-Prieto J, Villena-Gutiérrez R, Gómez M, Bernardo E, Pun-García A, García-Lunar I, Crainiciuc G, Fernández-Jiménez R, Sreeramkumar V, Bourio-Martínez R, García-Ruiz JM, Del Valle AS, Sanz-Rosa D, Pizarro G, Fernández-Ortiz A, Hidalgo A, Fuster V, Ibanez B. Neutrophil stunning by metoprolol reduces infarct size. *Nat Commun* 2017;**8**:14780.
41. Hagiwara S, Iwasaka H, Maeda H, Noguchi T. Landiolol, an ultrashort-acting beta1-adrenoceptor antagonist, has protective effects in an LPS-induced systemic inflammation model. *Shock* 2009;**31**:515–520.
42. Seki Y, Jesmin S, Shimojo N, Islam MM, Rahman MA, Khatun T, Sakuramoto H, Oki M, Sonobe A, Kamiyama J, Hagiya K, Kawano S, Mizutani T. Significant reversal of cardiac upregulated endothelin-1 system in a rat model of sepsis by landiolol hydrochloride. *Life Sci* 2014;**118**:357–363.
43. Ogura Y, Jesmin S, Yamaguchi N, Oki M, Shimojo N, Islam MM, Khatun T, Kamiyama J, Sakuramoto H, Hagiya K, Kawano S, Mizutani T. Potential amelioration of upregulated renal HIF-1alpha-endothelin-1 system by landiolol hydrochloride in a rat model of endotoxemia. *Life Sci* 2014;**118**:347–356.
44. Yoshino Y, Jesmin S, Islam M, Shimojo N, Sakuramoto H, Oki M, Khatun T, Suda M, Kawano S, Mizutani T. Landiolol hydrochloride ameliorates liver injury in a rat sepsis model by down regulating hepatic TNF-alpha. *Vasc Med Surg* 2015;**3**:1–5.
45. Matsuishi Y, Jesmin S, Kawano S, Hideaki S, Shimojo N, Mowa CN, Akhtar S, Zaedi S, Khatun T, Tsunoda Y, Kiwamoto T, Hizawa N, Inoue Y, Mizutani T. Landiolol hydrochloride ameliorates acute lung injury in a rat model of early sepsis through the suppression of elevated levels of pulmonary endothelin-1. *Life Sci* 2016;**166**:27–33.