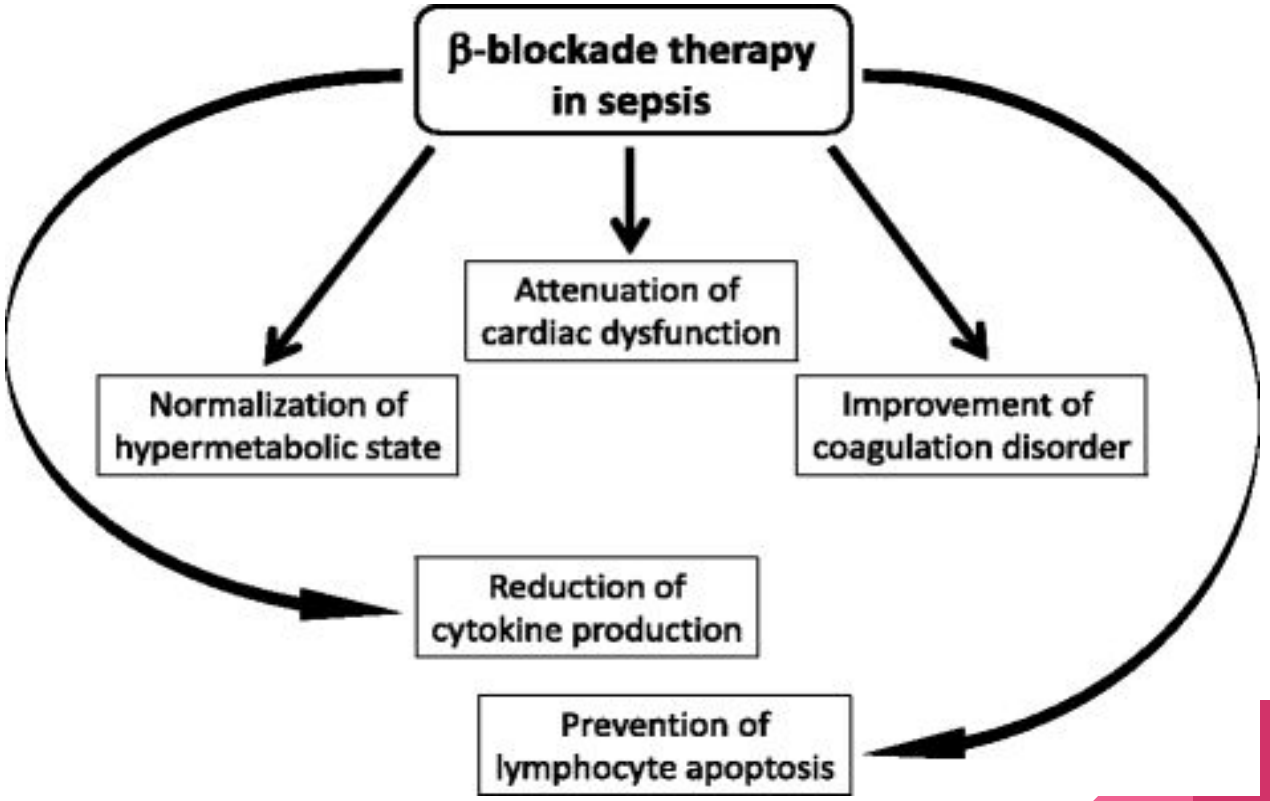
Landiolol and Organ Failure in Patients With Septic Shock: The STRESS-L Randomized Clinical Trial

Caring for the Crtically Ill Patient - JAMA 2023.

Physiopathology

Autonomic dysfunction and tachycardia are associated with poor outcomes in septic shock with reported mortality of more than 70% in some studies.

It’s true that the mechanisms by which B-Blockade may produce benefits are unknown, but it has been previously discussed and proved that Relative Bradycardia in patients undergoing adrenergic stress- affecting cardiac, immune, inflammatory and metabolic pathways- is associated with lower mortality and prevents the possible harmful effects of catecholamines.


β-blockade therapy in sepsis
Attenuation of cardiac dysfunction
Normalization of hypermetabolic state
Improvement of coagulation disorder
Reduction of cytokine production
Prevention of lymphocyte apoptosis

Key QUESTIONS

- Does B-blockade for up to 14 days reduce organ failure as measured by the Sequential Organ Failure Assessment (SOFA) score for critically ill patients with tachycardia and septic shock treated with high dose norepinephrine for more than 24 hours ?

- Why selecting the Landiolol as the acting B-Blocker for this study ?

Why selecting the Landiolol as the acting B-Blocker for this study ?

Two recent meta-analysis of respectively 8 and 7 randomized studies using Esmolol in patients with sepsis and septic shock suggested a 32% lower 28-mortality rate.

Landiolol is a very short-acting B-blocker and is approximately 8 times more selective for the B1-receptor than Esmolol.

Our Study hypothesis was that the additional B1-receptor specificity would bring about myocardial protection and immunomodulation to confer benefits to a high-risk population.

Setting and Intervention

POPULATION

74 Men 52 Women

Adults ≥18 years in intensive care unit (ICU) with septic shock receiving ≥0.1 µg/kg/min norepinephrine and heart rate ≥95/min

Mean age: 55.6 years

LOCATION

40 National Health Service ICUs in the UK

INTERVENTION

126 Patients randomized

63

Landiolol infusion

Continuous infusion during ICU stay of landiolol starting at 1.0 µg/kg/min and titrated to reach target heart rate

63

Standard care

Did not receive landiolol during stay in the ICU

PRIMARY OUTCOME

Mean SOFA score over the first 14 days after trial entry while in the ICU (SOFA score range, 0-20; higher score, worse organ dysfunction)

Results

Mortality at day 90 after randomization :

- 43.5% (27 of 62) >>>> the landiolol group
- 28.6% (18 of 63) >>>>the standard care group

There were no differences in the number of patients having at least one adverse event.

Conclusion

Among patients with septic shock with tachycardia and treated with norepinephrine for more than 24 hours, an infusion of landiolol did not reduce organ failure measured by the SOFA score over 14 days from randomization.

These results do not support the use of landiolol for managing tachycardia among patients treated with norepinephrine for established septic shock.

Further exploratory analyses?

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heart rate decrease, and ejection fraction decrease occurred in one patient each (1%).

Interpretation

Landiolol resulted in significantly more patients with sepsis-related tachyarrhythmia achieving a heart rate of 60–94 bpm at 24 h and significantly reduced the incidence of new-onset arrhythmia. Landiolol was also well tolerated, but it should be used under appropriate monitoring of blood pressure and heart rate owing to the risk of hypotension in patients with sepsis and septic shock.

Funding

Ono Pharmaceutical Co.

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Study into the reversal of septic shock with landiolol (beta blockade): STRESS-L Study protocol for a randomised trial

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Abstract

Introduction In 2013, a single-centre study reported the safe use of esmolol in patients with septic shock and tachycardia who required vasopressor therapy for more than 24 hours. Although not powered to detect a change in mortality, marked improvements were seen in survival (adjusted HR, 0.39; 95% CI, 0.26 to 0.59; p<0.001). Beta blockers are one of the most studied groups of drugs but their effect in septic shock is poorly understood; proposed mechanisms include not only the modulation of cardiac function but also immunomodulation.

Methods and analysis STRESS-L is a randomised, open-label, non-blinded clinical trial which is enrolling a total of 340 patients with septic shock as defined by Sepsis-3 consensus definition and a tachycardia (heart rate ≥95 beats per minute (bpm)) after