

# 38.

## BÖLÜM

## SEPSİS VE KALP

Onur GÖKÇE<sup>1</sup>  
Gülbin AYGENCEL<sup>2</sup>

### GİRİŞ

Sepsis, enfeksiyona karşı oluşan düzensiz konak tepkisinin neden olduğu yaşamı tehdit eden bir organ işlev bozukluğu olarak tanımlanır<sup>1</sup>. Tedavi yaklaşımındaki önemli ilerlemelere rağmen sepsis şu an koroner dışı yoğun bakımlarda en önemli ölüm nedenidir<sup>2,3</sup>.

Kardiyovasküler sistem, sepsis patogeneğinde önemli bir rol oynar. Sepsisteki miyokart disfonksiyonu, son elli yılda birçok çalışmanın odak noktası haline gelmiştir. Sepsis ilişkili kardiyomi-yopati (SIKMP) veya sepsis ilişkili miyokardiyal disfonksiyon (SIMD), septik hastalarda giderek daha çok tanınan geçici kardiyak disfonksiyonu tanımlamak için kullanılan terimlerdir. Septik kardiyomi-yopati (KMP)'nin varlığı organ işlev bozukluklarına önemli katkıda bulunur ve sepsis tanılı hastaların terapötik yönetimini daha da zorlaştırır. Kardiyovasküler sistemin karmaşıklığı, sayısız değerlendirme yöntemi ve kalbin sepsis öncesi durumundaki varyasyonlar, neden-sonuç ilişkisinin aydınlatılmasını zorlaştırır.

Sepsisin neden olduğu miyokardiyal disfonksiyonun klinik önemi hala belirsizdir. Sepsis sı-

rasında önyük, artyük ve nörohumoral değişikliklere verilen kardiyak cevap ile sepsisin kalp üzerindeki doğrudan etkisi arasında ayırım yapmak güçtür<sup>4</sup>.

Septik KMP'nin net ve tutarlı bir tanımının olmaması önemli bir sorundur. Bu durum, septik KMP'nin yaygınlığı ve prognostik önemi ile ilgili araştırmaları karmaşıklaştırmaktadır. Bu nedenle, kesin ve kanıta dayalı bir tanıma ihtiyaç duyulmaktadır.

Sepsis ilişkili KMP'nin ilk tanımlaması 1984 yılında Parker ve Parrillo tarafından yapılan çalışma sonrasında ortaya çıkmıştır. Bu çalışmada, tüm septik hastalarda normal veya artmış kardiyak indeks tespit edilmesine rağmen, hastaların %50'sinde ortalama sistol ve diyastol sonu hacimlerde artma ile birlikte azalmış sol ventrikül ejeksiyon fraksiyonu (EF) gözlemlenmiştir<sup>5</sup>. O zamandan beri SIKMP, birçok klinik araştırmada, her iki ventrikülün EF'sinde geri dönüşlü azalma, ventriküler genişleme, sıvı resüsitasyonuna ve katekolaminlere azalmış yanıt olarak tanımlanmıştır<sup>6</sup>. Buna rağmen, sol ventrikül EF'nin intrinsik miyokardiyal kasılma fonksiyonundan ziyade artyük ve kontraktilite arasın-

<sup>1</sup> Uzm. Dr., Gazi Üniversitesi Tıp Fakültesi, İç Hastalıkları AD, Yoğun Bakım BD, ogokce01@gmail.com

<sup>2</sup> Prof. Dr., Gazi Üniversitesi Tıp Fakültesi, İç Hastalıkları AD, Yoğun Bakım BD, aygencel@hotmail.com

Septik KMPLi hastalarda bu cihazların hem başarılı hem de başarısız kullanımına örnekler veren çok sayıda olgu sunumu vardır. Uygun destek cihazına karar vermeden önce dikkate alınması gereken noktalar sol ventrikül, sağ ventrikül veya biventriküler yetmezlik ve diastolik veya sistolik fonksiyon bozukluğu gibi hastaya özgü hemodinamiklerdir.

## SONUÇ

SIKMP önemli prognostik ve mortalite sonuçları olan ancak mevcut durumda yeterince tanınmayan sepsis ilişkili klinik bir durumdur. Klinisyenler, sepsis ilişkili organ disfonksiyonu ve septik şoku olan hastalarda, bu tanıyı dikkate almalıdır. Bazı biyobelirteçler prognostik bilgi sağlayabilir ve SIKMP tanısı için klinisyenin farkındalığını artırabilir; ancak tanısız faydaları kısıtlıdır. Ekokardiyografi şu anda altın standart tanı yöntemidir. Global longitudinal gerilimin değerlendirilmesi, SIKMP tanısı için solVEF veya diğer yaygın bulgulardan daha duyarlı ve özgündür. Tedavisi sepsis ve septik şokta olduğu gibi standart yönetim yani erken antibiyoterapi, vazopressörlerin, inotropoların ve makul sıvı resüsitasyonunun kullanımını içermektedir. Ek olarak, SIKMP yönetiminde diğer tedaviler için artan kanıtlar olmasına rağmen bunları günlük uygulamaya uyarlama konusunda kesin tavsiyelerde bulunmak için daha fazla veriye ihtiyaç vardır. Mevcut durumda tanı kriterlerine de ilişkin fikir birliği yoktur.

## KAYNAKLAR

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.
2. Holland EM, Moss TJ. Acute noncardiovascular illness in the cardiac intensive care unit. *Journal of the American College of Cardiology*. 2017;69(16):1999-2007.
3. Vincent JL, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *The Lancet Respiratory Medicine*. 2014;2(5):380-386.
4. Hochstadt A, Meroz Y, Landesberg G. Myocardial dysfunction in severe sepsis and septic shock: more questions than answers? *Journal of Cardiothoracic and Vascular Anesthesia*. 2011;25(3):526-535.
5. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Annals of Internal Medicine*. 1984;100(4):483-490.
6. Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J, J Huertos-Ranchal M. Sepsis-induced cardiomyopathy. *Current Cardiology Reviews*. 2011;7(3):163-183.
7. Lu NF, Jiang L, Zhu B, et al. Elevated plasma histone H4 levels are an important risk factor in the development of septic cardiomyopathy. *Balkan Medical Journal*. 2020;37(2):72.
8. Beesley SJ, Weber G, Sarge T, et al. Septic cardiomyopathy. *Critical Care Medicine*. 2018;46(4):625-634.
9. Sato R, Kuriyama A, Takada T, Nasu M, Luthe SK. Prevalence and risk factors of sepsis-induced cardiomyopathy: a retrospective cohort study. *Medicine*. 2016;95(39).
10. Jeong HS, Lee TH, Bang CH, Kim J-H, Hong SJ. Risk factors and outcomes of sepsis-induced myocardial dysfunction and stress-induced cardiomyopathy in sepsis or septic shock: A comparative retrospective study. *Medicine*. 2018;97(13):e0263.
11. Huang SJ, Nalos M, McLean AS. Is early ventricular dysfunction or dilatation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis. *Critical Care*. 2013;17(3):R96.



12. Orde SR, Pulido JN, Masaki M, et al. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. *Critical Care*. 2014;18(4):R149.
13. Sanfilippo F, Corredor C, Fletcher N, et al. Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis. *Critical Care*. 2018;22(1):183.
14. Vallabhajosyula S, Kumar M, Pandompatam G, et al. Prognostic impact of isolated right ventricular dysfunction in sepsis and septic shock: an 8-year historical cohort study. *Annals of Intensive Care*. 2017;7(1):94.
15. Feng M, McSparron JI, Kien DT, et al. Transthoracic echocardiography and mortality in sepsis: analysis of the MIMIC-III database. *Intensive Care Medicine*. 2018;44(6):884-892.
16. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell*. 2006;124(4):783-801.
17. Levy RJ, Piel DA, Acton PD, et al. Evidence of myocardial hibernation in the septic heart. *Critical Care Medicine*. 2005;33(12):2752-2756.
18. Antonucci E, Fiaccadori E, Donadello K, Taccone FS, Franchi F, Scolletta S. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. *Journal of Critical Care*. 2014;29(4):500-511.
19. Kakihana Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T. Sepsis-induced myocardial dysfunction: pathophysiology and management. *Journal of Intensive Care*. 2016;4(1):1-10.
20. Kumar A, Krieger A, Symeonides S, Kumar A, Parrillo JE. Myocardial dysfunction in septic shock: Part II. Role of cytokines and nitric oxide. *Journal of Cardiothoracic and Vascular Anesthesia*. 2001;15(4):485-511.
21. Pathan N, Hemingway CA, Alizadeh AA, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. *The Lancet*. 2004;363(9404):203-209.
22. Kelly RA, Balligand J-L, Smith TW. Nitric oxide and cardiac function. *Circulation Research*. 1996;79(3):363-380.
23. Lopfnov H, Werdan K, Reuter G, Flad H-D. The interleukin-1 and interleukin-1 converting enzyme families in the cardiovascular system. *European Cytokine Network*. 1999;9(4):675-680.
24. Francis SE, Holden H, Holt CM, Duff GW. Interleukin-1 in myocardium and coronary arteries of patients with dilated cardiomyopathy. *Journal of Molecular and Cellular Cardiology*. 1998;30(2):215-223.
25. Müller-Werdan U, Werdan K. Immune modulation by catecholamines—a potential mechanism of cytokine release in heart failure? *Herz*. 2000;25(3):271-273.
26. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. *Critical Care Medicine*. 2007;35(6):1599-1608.
27. Zanotti-Cavazzoni SL, Hollenberg SM. Cardiac dysfunction in severe sepsis and septic shock. *Current Opinion in Critical Care*. 2009;15(5):392-397.
28. Memiş D, Karamanlioğlu B, Turan A, Koyuncu O, Pamukçu Z. Effects of lornoxicam on the physiology of severe sepsis. *Critical Care*. 2004;8(6):1-9.
29. Konrad D, Oldner A, Rossi P, Wanecek M, Rudehill A, Weitzberg E. Differentiated and dose-related cardiovascular effects of a dual endothelin receptor antagonist in endotoxin shock. *Read Online: Critical Care Medicine | Society of Critical Care Medicine*. 2004;32(5):1192-1199.
30. Raeburn CD, Calkins CM, Zimmerman MA, et al. ICAM-1 and VCAM-1 mediate endotoxemic myocardial dysfunction independent of neutrophil accumulation. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2002;283(2):R477-R486.
31. Raeburn CD, Calkins CM, Zimmerman MA, et al. Vascular cell adhesion molecule-1 expression is obligatory for endotoxin-induced myocardial neutrophil accumulation and contractile dysfunction. *Surgery*. 2001;130(2):319-325.
32. Niederbichler AD, Hoesel LM, Westfall MV, et al. An essential role for complement C5a in the pathogenesis of septic cardiac dysfunction. *The Journal of Experimental Medicine*. 2006;203(1):53-61.
33. Alhamdi Y, Abrams ST, Cheng Z, et al. Circulating histones are major mediators of cardiac injury in patients with sepsis. *Critical Care Medicine*. 2015;43(10):2094-2103.
34. VanPatten S, Al-Abed Y. High mobility group box-1 (HMGB1): current wisdom and advancement as a potential drug target: miniperspective. *Journal of Medicinal Chemistry*. 2017;61(12):5093-5107.

35. Carré JE, Singer M. Cellular energetic metabolism in sepsis: the need for a systems approach. *Biochimica et Biophysica Acta (BBA)-Bioenergetics*. 2008;1777(7-8):763-771.
36. Jang DH, Greenwood JC, Spyres MB, Eckmann DM. Measurement of mitochondrial respiration and motility in acute care: sepsis, trauma, and poisoning. *Journal of Intensive Care Medicine*. 2017;32(1):86-94.
37. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *The Lancet*. 2002;360(9328):219-223.
38. Potz BA, Sellke FW, Abid MR. Endothelial ROS and impaired myocardial oxygen consumption in sepsis-induced cardiac dysfunction. *Journal of Intensive and Critical Care*. 2016;2(1):20.
39. Larsen FJ, Schiffer TA, Weitzberg E, Lundberg JO. Regulation of mitochondrial function and energetics by reactive nitrogen oxides. *Free Radical Biology and Medicine*. 2012;53(10):1919-1928.
40. Crouser ED. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. *Mitochondrion*. 2004;4(5-6):729-741.
41. Kayali R, Aydin S, Çakataş U. Effect of gender on main clinical chemistry parameters in aged rats. *Current Aging Science*. 2009;2(1):67-71.
42. Lowes D, Webster N, Murphy M, Galley H. Antioxidants that protect mitochondria reduce interleukin-6 and oxidative stress, improve mitochondrial function, and reduce biochemical markers of organ dysfunction in a rat model of acute sepsis. *British Journal of Anaesthesia*. 2013;110(3):472-480.
43. Bernardi P, Di Lisa F. The mitochondrial permeability transition pore: molecular nature and role as a target in cardioprotection. *Journal of Molecular and Cellular Cardiology*. 2015;78:100-106.
44. Hassoun SM, Marechal X, Mouton R, et al. Prevention of endotoxin-induced sarcoplasmic reticulum calcium leak improves mitochondrial and myocardial dysfunction. *Critical Care Medicine*. 2008;36(9):2590-2596.
45. Smeding L, Plötz FB, Groeneveld AJ, Kneyber MC. Structural changes of the heart during severe sepsis or septic shock. *Shock*. 2012;37(5):449-456.
46. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell*. 2012;148(6):1145-1159.
47. Harrington J, Choi AM, Nakahira K. Mitochondrial DNA in sepsis. *Current Opinion in Critical Care*. 2017;23(4):284.
48. Nakahira K, Haspel JA, Rathinam VA, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nature Immunology*. 2011;12(3):222-230.
49. Nakahira K, Kyung S-Y, Rogers AJ, et al. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. *PLoS Med*. 2013;10(12):e1001577.
50. Sánchez-Villamil JP, D'Annunzio V, Finocchietto P, et al. Cardiac-specific overexpression of thioredoxin 1 attenuates mitochondrial and myocardial dysfunction in septic mice. *The International Journal of Biochemistry and Cell Biology*. 2016;81:323-334.
51. Liesa M, Palacín M, Zorzano A. Mitochondrial dynamics in mammalian health and disease. *Physiological Reviews*. 2009;89(3):799-845.
52. Zhan M, Brooks C, Liu F, Sun L, Dong Z. Mitochondrial dynamics: regulatory mechanisms and emerging role in renal pathophysiology. *Kidney International*. 2013;83(4):568-581.
53. Wu Y, Yao Y-M, Lu Z-Q. Mitochondrial quality control mechanisms as potential therapeutic targets in sepsis-induced multiple organ failure. *Journal of Molecular Medicine*. 2019;97(4):451-462.
54. Gunst J, Derese I, Aertgeerts A, et al. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. *Critical Care Medicine*. 2013;41(1):182-194.
55. Bosch NA, Cohen DM, Walkey AJ. Risk factors for new-onset atrial fibrillation in patients with sepsis: a systematic review and meta-analysis. *Critical Care Medicine*. 2019;47(2):280-287.
56. Adler A, Topaz G, Heller K, et al. Fever-induced Brugada pattern: how common is it and what does it mean? *Heart Rhythm*. 2013;10(9):1375-1382.
57. Bessière F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. *Intensive Care Medicine*. 2013;39(7):1181-1189.
58. Martin L, Derwall M, Al Zoubi S, et al. The septic heart: current understanding of molecular mechanisms and clinical implications. *Chest*. 2019;155(2):427-437.



59. Vasques-Nóvoa F, Laundos TL, Madureira A, et al. Myocardial edema: an overlooked mechanism of septic cardiomyopathy? *Shock*. 2020;53(5):616-619.
60. Charpentier J, Luyt C-E, Fulla Y, et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. *Critical Care Medicine*. 2004;32(3):660-665.
61. Ehrman RR, Sullivan AN, Favot MJ, et al. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature. *Critical Care*. 2018;22(1):112.
62. Vieillard-Baron A, Millington S, Sanfilippo F, et al. A decade of progress in critical care echocardiography: a narrative review. *Intensive Care Medicine*. 2019;45(6):770-788.
63. Repessé X, Charron C, Vieillard-Baron A. Evaluation of left ventricular systolic function revisited in septic shock. *Critical Care*. 2013;17(4):1-4.
64. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal-Cardiovascular Imaging*. 2015;16(3):233-271.
65. Gajanana D, Seetha Rammohan H, Alli O, et al. Tricuspid annular plane systolic excursion and its association with mortality in critically ill patients. *Echocardiography*. 2015;32(8):1222-1227.
66. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine*. 2006;174(9):1034-1041.
67. Furian T, Aguiar C, Prado K, et al. Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. *Journal of Critical Care*. 2012;27(3):319.e319-319. e315.
68. Landesberg G, Gilon D, Meroz Y, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. *European Heart Journal*. 2012;33(7):895-903.
69. Sibbald WJ, Paterson NM, Holliday RL, Anderson RA, Lobb TR, Duff JH. Pulmonary hypertension in sepsis: measurement by the pulmonary arterial diastolic-pulmonary wedge pressure gradient and the influence of passive and active factors. *Chest*. 1978;73(5):583-591.
70. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Journal of Echocardiography*. 2016;17(12):1321-1360.
71. Sanfilippo F, Corredor C, Arcadipane A, et al. Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: a systematic review and meta-analysis. *BJA: British Journal of Anaesthesia*. 2017;119(4):583-594.
72. Ng PY, Sin WC, Ng AK-Y, Chan WM. Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS). *Critical Care*. 2016;20(1):145.
73. Vallabhajosyula S, Rayes HA, Sakhuja A, Murad MH, Geske JB, Jentzer JC. Global longitudinal strain using speckle-tracking echocardiography as a mortality predictor in sepsis: a systematic review. *Journal of Intensive Care Medicine*. 2019;34(2):87-93.
74. Chauvet J-L, El-Dash S, Delastre O, et al. Early dynamic left intraventricular obstruction is associated with hypovolemia and high mortality in septic shock patients. *Critical Care*. 2015;19(1):262.
75. Mosier JM, Stolz U, Milligan R, et al. Impact of point-of-care ultrasound in the emergency department on care processes and outcomes in critically ill nontraumatic patients. *Critical Care Explorations*. 2019;1(6).
76. Harvey S, Young D, Brampton W, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database of Systematic Reviews*. 2013(2):CD003408.
77. Werdan K, Oelke A, Hettwer S, et al. Septic cardiomyopathy: hemodynamic quantification, occurrence, and prognostic implications. *Clinical Research in Cardiology*. 2011;100(8):661-668.
78. Wilhelm J, Hettwer S, Schuermann M, et al. Severity of cardiac impairment in the early stage of community-acquired sepsis determines worse prognosis. *Clinical Research in Cardiology*. 2013;102(10):735-744.
79. Fernandez-Mondejar E, Guerrero-Lopez F, Colmenero M. How important is the measurement of extravascular lung water? *Current Opinion in Critical Care*. 2007;13(1):79-83.

80. Monnet X, Anguel N, Naudin B, Jabot J, Richard C, Teboul J-L. Arterial pressure-based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. *Critical Care*. 2010;14(3):1-11.
81. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Medicine*. 2017;45(3):486-552.
82. Li H, Xing Y, Yang D, Tang X, Lu D, Wang H. Alpha-1 adrenergic receptor agonist phenylephrine inhibits sepsis-induced cardiomyocyte apoptosis and cardiac dysfunction via activating ERK1/2 signal pathway. *Shock*. 2019;52(1):122-133.
83. Nadeem R, Sockanathan S, Singh M, Hussain T, Kent P, AbuAlreesh S. Impact of dobutamine in patients with septic shock: a meta-regression analysis. *American Journal of Therapeutics*. 2017;24(3):e333-e346.
84. Hernandez G, Bruhn A, Luengo C, et al. Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. *Intensive Care Medicine*. 2013;39(8):1435-1443.
85. Gattinoni L, Brazzi L, Pelosi P, et al. for the SvO2 Collaborative Group. A trial of goal-oriented hemodynamic therapy in critically ill patients. *New England Journal of Medicine*. 1995;333:1025-1032.
86. Schmittinger CA, Dünser MW, Haller M, et al. Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. *Critical Care*. 2008;12(4):R99.
87. Morelli A, De Castro S, Teboul JL, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Medicine*. 2005;31(5):638-644.
88. Zangrillo A, Putzu A, Monaco F, et al. Levosimendan reduces mortality in patients with severe sepsis and septic shock: a meta-analysis of randomized trials. *Journal of Critical Care*. 2015;30(5):908-913.
89. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. *New England Journal of Medicine*. 2016;375(17):1638-1648.
90. Macchia A, Romero M, Comignani PD, et al. Previous prescription of  $\beta$ -blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis. *Critical Care Medicine*. 2012;40(10):2768-2772.
91. De Santis V, Frati G, Greco E, Tritapepe L. Ivabradine: a preliminary observation for a new therapeutic role in patients with multiple organ dysfunction syndrome. *Clinical Research in Cardiology*. 2014;103(10):831-834.
92. Nuding S, Schröder J, Presek P, et al. Reducing elevated heart rates in patients with multiple organ dysfunction syndrome with the if (funny channel current) inhibitor ivabradine. *Shock*. 2018;49(4):402-411.
93. Lo JC, Darracq MA, Clark RF. A review of methylene blue treatment for cardiovascular collapse. *The Journal of Emergency Medicine*. 2014;46(5):670-679.
94. Gabel E, Gudzenko V, Cruz D, Ardehali A, Fink MP. Successful use of extracorporeal membrane oxygenation in an adult patient with toxic shock-induced heart failure. *Journal of Intensive Care Medicine*. 2015;30(2):115-118.
95. Pořízka M, Kopecký P, Prskavec T, Kunstýř J, Rulišek J, Balík M. Successful use of extracorporeal membrane oxygenation in a patient with streptococcal sepsis: a case report and review of literature. *Prague Medical Report*. 2015;116(1):57-63.
96. Bréchet N, Luyt C-E, Schmidt M, et al. Venous arterial extracorporeal membrane oxygenation support for refractory cardiovascular dysfunction during severe bacterial septic shock. *Critical Care Medicine*. 2013;41(7):1616-1626.
97. Park TK, Yang JH, Jeon K, et al. Extracorporeal membrane oxygenation for refractory septic shock in adults. *European Journal of Cardio-Thoracic Surgery*. 2015;47(2):e68-e74.
98. Baumgartner J, Vaney C, Perret C. An extreme form of the hyperdynamic syndrome in septic shock. *Intensive Care Medicine*. 1984;10(5):245-249.