Abstract

Sepsis, or life-threatening organ dysfunction caused by deregulated host response to the presence of infection, is one of the most significant causes of death caused by infection diseases worldwide. 31.5 million patients get sick with sepsis annually and 5.3 million of them die. Sepsis is characterised by homeostatic dysbalance, which can lead to septic shock or even to death. Sepsis may also result in development of multiorgan dysfunction or damage to several organs at the same time. Especially heart, kidneys, liver, lungs, central nervous system and blood elements belong among the organs affected by sepsis. One of the most affected organs is the heart, impairment of which is accompanied with the development of myocardial depression, which contributes to the increase of mortality from sepsis. The precise mechanisms leading to septic myocardial depression have not been fully explained yet, nevertheless mitochondria appear to play an important role in this process. Due to sepsis, many mitochondrial functions are disrupted, which is subsequently manifested by the depletion of cellular energy stores, resulting in myocardial depression.

In our laboratories, we managed to create a clinically relevant model of sepsis and septic shock, specifically sepsis caused by fecal peritonitis in domestic pigs, that allowed us to study the cellular mechanisms of sepsis, septic myocardial depression and especially the role of mitochondria in these processes focusing on mitochondrial respiration. In our research, it was shown that sepsis causes a decrease of mitochondrial respiration in the permeabilized fibers of the left ventricle, in particular at the level of complexes II and IV. On the same experimental model, the effects of two therapeutic approaches were subsequently investigated, namely the effect of vagus nerve stimulation and the application of mesenchymal stem cells on hemodynamic parameters, organ and mitochondrial functions. We were the first to prove, that stimulation of the vagus nerve has a number of beneficial effects on the course of sepsis in pigs, especially on the functions of the cardiovascular system and energy metabolism. Stimulation of the vagus nerve partially or completely prevented the developement of hyperlactatemia, hyperdynamic circulation, myocardial cells depression, it led to a significant decrease in SOFA score (sequential score of organ failure assessment) and also reversed the decrease in mitochondrial respiration of permeabilized left ventricular muscle fibers caused by sepsis. Therefore, the obtained data indicate a promising therapeutic potential of the vagus nerve stimulation in sepsis or septic shock. However, in our porcine model of sepsis, no beneficial effects of mesenchymal stem cell administration

on sepsis-induced myocardial depression, deregulated immune and inflammatory response, or mitochondrial dysfunction were demonstrated. Application of mesenchymal stem cells failed to reverse the inhibition of mitochondrial respiration of the complex II or the decrease in complex IV activity of permeabilized left ventricular muscle fibres induced by sepsis. However, a beneficial effect of the application of these cells in other organs or on other mitochondrial parameters, which were not the subject of our research, cannot be ruled out.

Keywords: sepsis, septic myocardial depression, mitochondria, mitochondrial dysfunction, high resolution respirometry, vagus nerve, mesenchymal stem cells