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Novel Therapeutic Targets in Severe Shock Treatment

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Abstract

Severe or irreversible shock is a final stage of shock. After treatment of severe shock still exist persistent low microcirculatory perfusion, refractory hypotension, and cell injury, which are 3 main pathogenesis factors and should be looking for new approach to treat it. It has shown that some new therapeutic targets are related to the treatment of the 3 factors, which includes pulse pressure with persistent low perfusion, ASMCs hyperpolarization with refractory hypotension, mitochondrial dysfunction with cell injury, SIRT1 activity with mitochondrial dysfunction. A new anti- shock medicine-polydatin has effected on these new therapeutic targets, which has been going to clinical trial in China and America.

Keywords: severe shock, pulse pressure, low microcirculatory perfusion, refractory hypotension, mitochondrial dysfunction, SIRT1 activity

Introduction

Severe or irreversible shock is a final stage of shock, during which the anti-shock treatment including infusion or transfusion, vasoactive agent, cardiotonic drug, etc, is generally ineffective [1,2]. Therefore, it is important to look for a new approach in the treatment of severe shock. After treatment of shock still exist persistent low microcirculatory perfusion, refractory hypotension and cell injury even MODS, which are 3 main factors in the pathogenesis of severe shock (Figure 1). The works in our lab were focused on the 3 genesis factors in the past 50 years [3], during which following therapeutic targets were found in the treatment of severe shock.

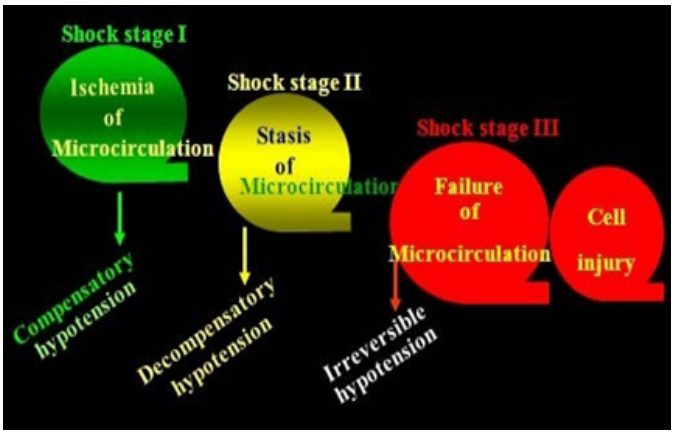

Figure 1.Three pathogenesis factors in severe shock (shock stage III) [3].

Pulse pressure in treatment of persistent low perfusion

Persistent low perfusion is a major events in the pathogenesis of severe shock [6,7]. Capillary no reflow post treatment of shock was first observed in animal models, but it was recently confirmed in patient with myocardial infarction, which indicated that functional capillary density (FCD) was an independent predictor of death [8,9,10,11]. One of the causes for persistent low perfusion (no-reflow) is leukocyte adhesion on venule walls and plugging in capillaries, which comes from the low wall shear stress and high leukocyte-endothelial adhesion force in severe shock [12,13,14]. However, blockade of leukocyte adhesion by monoclonal antibodies could only attenuate the number of sticking WBC in venules, but couldn't make an appreciable improvement of capillary reflow and survival rate in severe shock [6,15,16], because it was difficult for the agent to flow into an obstructed capillary. Since the chemical agent can't enter and pass through an occluded capillary, the only way which can put through the capillary is to look for a mechanic force to abolish trapped leukocyte in the capillary.

Administration of PD led to an increase of pulse pressure to more than pre- hemorrhage level. Using 2 cameras recording technique (one for recording blood pressure on the screen of a dynograph, another for recording microcirculation under a microscope), a pulsatile blood movement synchronous with the widening of pulse pressure fluctuation occurred in the opening of capillary. The pulsatile excursion of blood acted to dislodge the entrapped leukocyte and stationary red blood cells away, which led to capillary reflow with an increased survival rate [16,17,18,19].

Polydatin (PD) is a monomer product, which chemical structure is trans-3,4'5- trihydroxystibene-3-D- monoglucoside [3,4,5]. PD has been given the permission by the Chinese FDA (CFDA Approval number 2006100301) and the America FDA (Clinical trials gov. Identifier NCTO 1780129) to clinical trial in China and America. The increase of pulse pressure results in the pulsatile blood motion at the entry of capillaries with blood reflow in shock. Polydatin leads to dilate microvessels and reduce leukocyte adhesion with the reduction of total peripheral resistance (TPR) in shock. Polydatin also can improve reduced heart function in shock, which was demonstrated with measurement of left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEP), maximal rate of the increase or decrease of the left ventricular pressure (±dp/dt max), and the cardiac output (CO) [19,20,21]. Both effect of PD on heart function and the microcirculation leads to the recovery and enhancement of pulse pressure in severe shock. It has been shown recently that polydatin has multiple therapeutic effects on cell injury of severe shock, including protection against mitochondrial dysfuction, an agonist of SIRT1/3, suppression of oxidative stress, inhibition of proinflammatory cytokines, attenuation of apoptosis, and allevation of histopathology change in MODS rat [32-44].

ASMCs Hyperpolarization in treatment of refractory hypotension

One of the hall marks in severe shock is refractory hypotension. It has been reported that metabolites accumulation, energy exhaustion, desensitization of adrenergic receptors, and the effect of cytokines (NO, ET, etc) were thought to involve in the genesis of shock hypotension [6]. However, the final pathway of refractory hypotension is the low responsiveness of arteriolar smooth muscle cells (ASMCs) to contraction by intrinsic and extrinsic vasoconstrictors. It was shown by us that the resting potential of ASMCs increased from pre-bleeding value of -36.7±6.3mV to -51.0±9.1mV at 2 h post shock, indicating the appearance of ASMC hyperpolarization in severe shock [6,22].

Meanwhile the NE threshold concentration for an A3 arteriole contraction increased 15 times more than the pre bleeding value, indicating appearance of low vasoreactivity in severe shock. ASMC hyperpolarization led to inhibition of the potential operated calcium channel (POC) or Lca^{2+} channel, resulting in a reduction of the $[Ca^{2+}]i$ of ASMCs stimulated by NE. The level of increased $[Ca^{2+}]i$ in ASMCs following NE stimulation in shock group was only 50.1% of the value in the control group, which could finally lead to decreased vessel contraction [6,23,24].

Potassium channels represent the domination conductance of vascular smooth muscle membranes, play a major role in the regulation of membrane potential, and participate in the mechanism of arteriolar wall contraction. It was shown that the ATP-sensitive potassium channel (K_{ATP}) in ASMC was activated by intracellular ATP depletion and intracellular acidosis, and the large conductance calcium-activated potassium channel (BK_{Ca}) of ASMCs was also activated by the enhanced calcium spark and $ONOO^-$ action in severe shock [23-29]. According to the work mentioned above, a schema for the role of ASMCs hyperpolarization and K^+ channel activation in the genesis of low vasoreactivity was figured out (Figure 2).

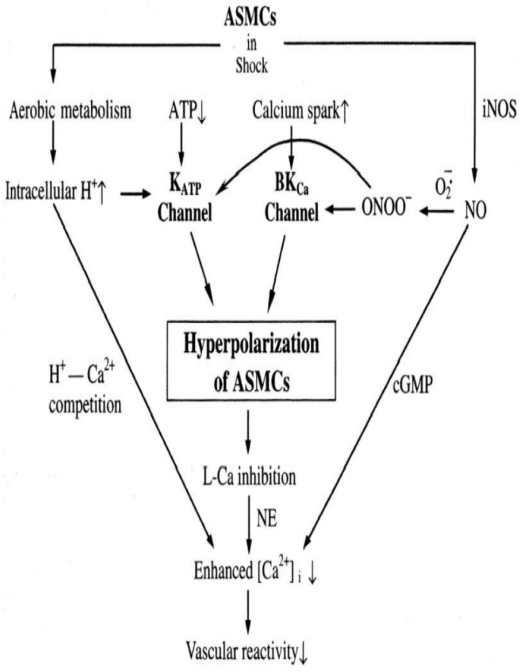

Figure 2. The schema for the etiology of vascular hyporeactivity in severe shock [3]

Based on the schema, 4 medicines were used in vivo for treatment of severe shock, which included glybenclamide (blocker of K_{ATP} channel), iberiotorin and charybdotoxin (blockers of BK_{Ca} channels), and bay K8644 (activator of POC or Lca^{2+} channel). Of the 4 drugs, only glybenclamide could prolong the survival rate in rat with severe hemorrhagic shock (1/8 vs 7/8 survival for 24 h in shock group and shock+glyben group respectively), and the others could transiently enhance the blood pressure, but animal died later because of the toxic effects of the drugs. Therefore, a new approach to treatment of severe shock was put forward, that is administration of restituting vasoreactivity agent (glybenclamide) first, followed by giving vasopressor (NE or dopamine) [30].

Mitochondrial dysfunction in treatment of cell injury

As mentioned above, the ATP depletion of ASMCs in severe shock led to activation of K_{ATP} channels with ASMCs hyperpolarization and persistent hypotension. The depressed ATP level existed even after administration of infusion, transfusion, and vasoactive agent with improvement of microcirculation, which indicated that low ATP level might not only result from insufficient delivery of nutrient and oxygen, but also from the damage of ATP factory- mitochondrial dysfunction (MD) [31]. The evidence of MD in ASMCs includes mitochondria damage (mitochondria swollen with poorly defined crystae (Figure 3), mitochondrial transition pore (mPTP) opening, mitochondrial transmembrane potential ($\Delta\psi m$) reducing, and intracellular ATP content lowering. Mitochondrial damage could partially protected by mitochondrial protector (cyclosporine A CsA, resveratrol RVS, polydatin PD) [31-33]. Severe shock caused significant decrease the intracellular ATP level of ASMC to 17.6±7.9% of the control value , which led to activation of K_{ATP} channels and hyperpolarization of ASMCs and finally led to low vasoreactivity and persistent hypotension in severe shock. Polydatin could protect mitochondrial damage and restore ASMCs ATP content to 89.57±9.21% of the control value with restitution of vasoreactivity [31-33].

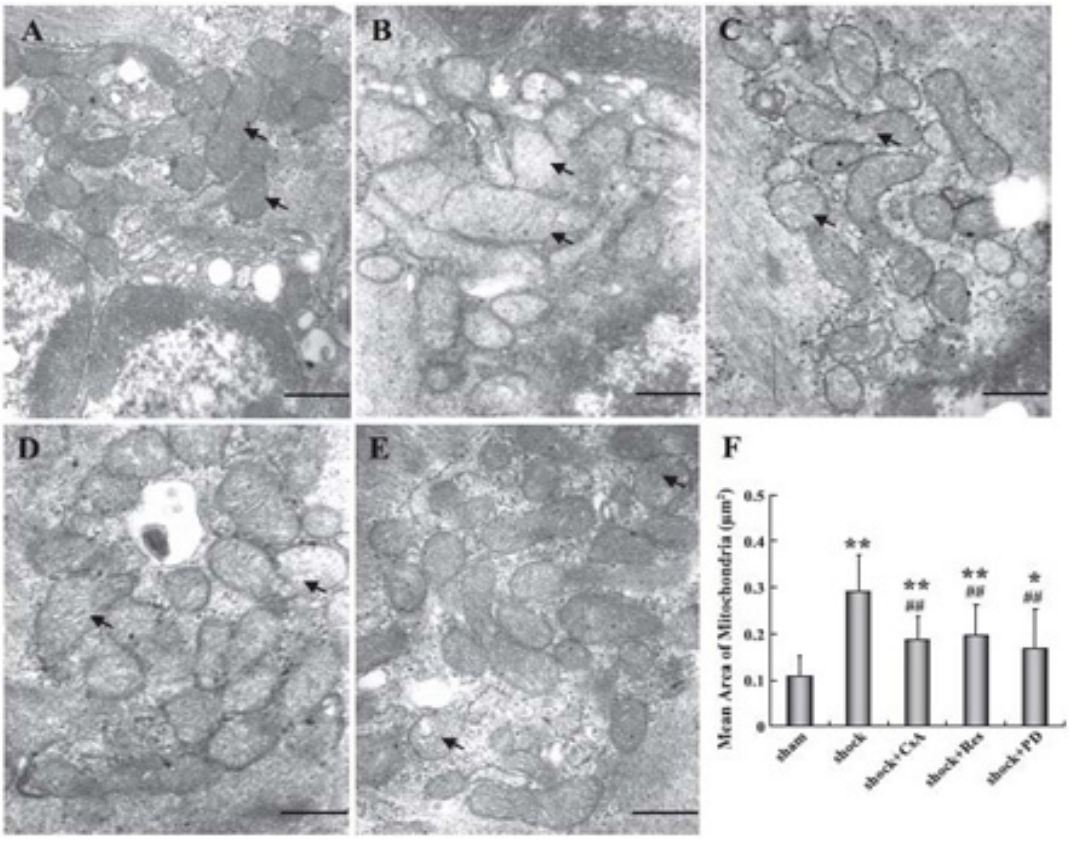

Figure 3. Ultrastructural alterations of ASMC mitochondria in severe shock [3]. A: normal mitochondria (some arrowed) in the control group. B: mitochondria swollen with poorly defined crystae in the shock group. These alterations are partially prevented in the shock + CsA (C), shock + RVS (D), and shock + PD groups (E), respectively. Scale bars: 1.0μm.

Besides ASMCs, mitochondrial dysfunction also existed in diverse organs of severe shock, including brain neurons (BN), pulmonary arteriolar muscle cells (PASMCs), renal tubular epithelial cell (RTEC), small intestine epithelial (SIP), hepatocytes, platelets, etc [32,33,34,35]. Therefore, mitochondrial and cellular injury are a common pathway in severe shock [36,37].

SIRT1/3 activity in treatment of mitochondrial dysfunction

The pathogenesis factors of mitochondrial dysfunction in severe shock includes free radicals, calcium over load, casepsin of lysosome, etc. It was shown by us that protein acetylation was an important cause for mitochondrial and cellular injury in severe shock. It was shown that sirtuin (SIRT1/3) protein level and deacetylase activity were significantly decrease in many organs during severe hemorrhagic shock [39-45]. Based on reduced SIRT1/3 activity, three kind of mitochondria-related protein (CypD, SOD_2, p53) would be over-acetylated, which led to mPTP opening, more ROS production, and P53 transcription- independent apoptosis in severe shock respectively [37], although the mechanism of SIRT down regulation in shock remains to be explored. Polydatin (PD) and resveratrol (RSV) may serve as an activator of SIRT1/3 (Figure 4).

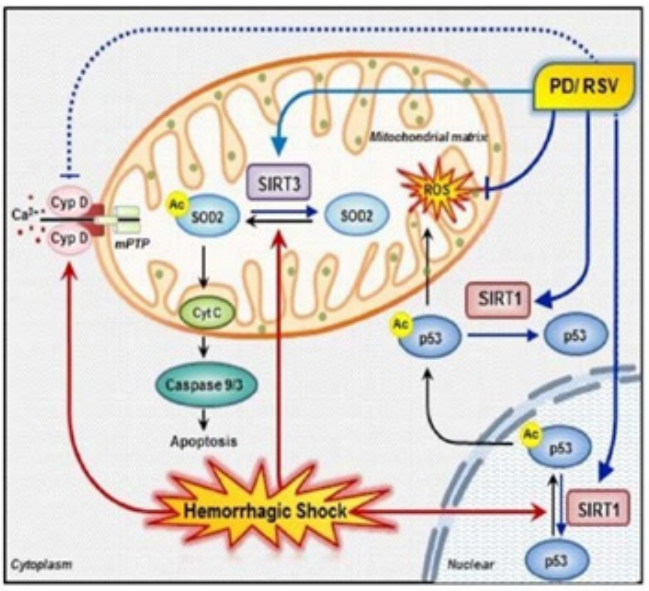

Figure 4 $SIRT_{1/3}$ low activity with over acetylation of mitochondrial-related protein in shock [3]

Mitochondrial injury may lead to energy exhaustion with ROS production, release of apoptosis enzymes, and calcium overload, which finally results in cell death. The cell injury appears with no apparent signs in severe shock and it is too late to recognize it until organ failure. According to our works, refractory hypotension post treatment and platelet MD from blood test indicate appearance of cell injury in severe shock, during which the patient should be treated with MD protective medicines, including drugs for provision of mitochondrial substrate and cofactors, reduction of mitochondrial ROS production, inhibition of MPTP opening, activation of SIRT1/3, etc [37]. In summary, pulse pressure, ASMCs hyperpolarization, mitochondrial and cell damage, SIRT1 activity may serve as a new therapeutic target in severe shock treatment.

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