5. The significance of mitochondrial biogenesis reprogramming in refractory hypotension and multi-organ dysfunction during hemorrhagic shock

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Abstract. Refractory hypotension following vascular hyporeactivity and multi-organ dysfunction are the major causes of mortality from severe shock and resuscitation in the clinic. Depressed contractile vasoresponsiveness and persistent hypotension not only result from insufficient microcirculatory delivery of nutrients and oxygen but also from mitochondria-derived cytopathic hypoxia. Our studies identified that mitochondrial dysfunction in arteriolar smooth muscle cells is involved in the pathogenesis of low vasoresponsiveness during hemorrhagic shock. Mitochondrial injury was also found in organ dysfunction. However, the molecular mechanism underlying mitochondria injury in the progression of hemorrhagic shock remains elusive. Discovery of mitochondrial biogenesis reprogramming and energy...
metabolism regulation provides new insights into the mechanisms of mitochondrial damage and mitochondrial-mediated human diseases or pathologic conditions. Recently, energizing genetics and epigenetics play important role in the regulation of mitochondrial function. Histone deacetylases have been demonstrated to dramatically improve survival following lethal hemorrhagic shock, thereby providing a potential link between hemorrhagic shock injury and epigenetic regulation. The aim of this review is to highlight the role of epigenetics in multi-organ mitochondrial biogenesis reprogramming and discuss the potential of mitochondria based therapeutic approaches for the management and treatment of refractory hypotension and multi-organ dysfunction following hemorrhagic shock.

Introduction

Mitochondria is crucial in the pathogenesis of refractory hypotension and multi-organ dysfunction during hemorrhagic shock [1-6], and the relevant mechanisms of mitochondrial dysfunction in ischemic disorders have been extensively studied [1, 2, 4-8]. More importantly, our recent studies showed that histone deacetylase sirtuin 1 (SIRT1) plays a crucial role in mitochondrial biogenesis and function [2, 4, 6]. Resveratrol, frequently used as a SIRT1 activator, restored the activities of SIRT1 and mitochondrial complex in the arteriolar smooth muscle, liver, kidney and heart [2, 4, 9, 10]. These indicated that mitochondrial biogenesis reprogramming was not only strongly implicated in the progression of refractory hypotension and multi-organ dysfunction, but could also define the protective or toxic properties of other drugs following hemorrhagic shock.

Mitochondrial biogenesis is the process by which cells increase their individual mitochondrial mass and copy number to increase the production of adenosine triphosphate (ATP) as a response to greater energy expenditure [11, 12]. Mitochondrial biogenesis was first defined by Holloszy when he found physical endurance training can induce higher levels of mitochondrial content, which cause greater glucose uptake by muscles [13]. Mitochondrial biogenesis is activated by many cellular and molecular processes in response to environmental or intracellular stress, including exercise, caloric restriction, low temperature, oxidative stress, and cell division, renewal, and differentiation [14]. Mitochondrial proteins are most produced from the nuclear genome, while the mitochondrial DNA (mtDNA) encodes components of the electron transport chain (ETC) and scrambled fragments of ribosomal RNA. Upregulation of mitochondrial
Mitochondrial biogenesis reprogramming in shock

Mitochondrial biogenesis augments metabolic enzymes for glycolysis, oxidative phosphorylation and thus a greater mitochondrial metabolic capacity. Achieving a balance between the mechanisms in mitochondrial metabolic checkpoint contributes to the appropriate network of mitochondrial biogenesis in different cells adaptation to environmental stress [15]. Mitochondrial biogenesis has been demonstrated to be decreased with aging, and such decreased mitochondrial function is associated with diabetes and cardiovascular diseases [16-18]. Recently, we have reported that mitochondrial biogenesis and function are altered and regulated in various cell types and tissues during hypoxia/reoxygenation and hemorrhagic shock [1-6, 19].

The purpose of this review is to give a brief overview of the role of mitochondrial biogenesis reprogramming in relation to hemorrhagic shock injury and to suggest new insights into how epigenetic mechanism in mitochondrial injury, and mitochondria-based therapeutic approaches for treatment of refractory hypotension and multi-organ dysfunction during hemorrhagic shock and related disorders.

1. Mitochondria and hemorrhagic shock

Mitochondria are extremely specialized organelles that generate ATP via the ETC and oxidative phosphorylation system (OXPHOS). They are essential for maintaining energy homeostasis in different kinds of cells. Growing evidence suggests that mitochondrial dysfunction plays a key role in the pathogenesis of ischemia and reperfusion injury and cardiomyopathy [20, 21]. Intriguingly, it has been reported that the developmental process of mitochondrial deterioration in hemorrhagic shock can be divided into four stages: 1) initially greatly decreased the cellular energy level due to marked energy consumption without any organic damages in the mitochondria, 2) cellular energy imbalance due to the depressed mitochondrial activity in vivo, which was reversible when the blood supply was restored, 3) severely increased mitochondrial fragility, 4) markedly organically damaged mitochondria and cellular energy metabolism, which were not remedied by any intensive therapies, leading to the failure of vital organs [22]. These findings are consistent with what we have found in mesenteric arteriolar smooth muscle cells (ASMCs) that hemorrhagic shock led to a progressive damage in mitochondrial function and morphology (Fig. 1) [2].
In our reproduced hemorrhagic shock model with 2 h hemorrhage to keep mean arterial pressure (MAP) at 30 mmHg and 2 h observation after reinfusion of shed blood, we found mitochondrial dysfunction involving the functional (ATP), morphologic (ultrastructure damage), and metabolic (mitochondrial permeability transition pore, mPT pore and mitochondrial membrane potential, ΔΨm) aspects in ASMCs (Fig. 1), which are critical in the genesis of refractory hypotension during irreversible hemorrhagic shock [1-3]. However, the cellular and molecular mechanisms of mitochondrial biogenesis reprogramming and mitochondrial dysfunction underlying the progression of severe hemorrhagic shock is poorly understood.

2. Mitochondrial biogenesis reprogramming in refractory hypotension

Mitochondrial dysfunction with a defective oxidative metabolism and a low mitochondrial gene expression were evident in ischemia and reperfusion
Mitochondrial biogenesis reprogramming in shock [23], suggesting that hemorrhagic shock and related disorders are linked to defective mitochondrial biogenesis and oxidative metabolism with a decreased ATP production. Recent studies in shock-damaged ASMCs have supported this hypothesis, not only at the molecular and biochemical but also at the morphological level [1-3]. It has been demonstrated that the depletion of ATP in ASMCs in severe shock led to the activation of ATP-sensitive potassium channels with hyperpolarization of ASMCs, which subsequently inhibited L-type Ca^{2+} channels in norepinephrine-stimulated ASMCs [24]. The consequently reduced Ca^{2+} influx resulted in depression of contractile vasoresponsiveness and persistent hypotension. Our successive studies further demonstrated that insufficient delivery of nutrients and oxygen and mitochondria dysfunction seemed to be responsible for the diminished ATP level [1-3]. We measured mitochondrial ultrastructure and function by using freshly isolated ASMCs. In the shock group, it was shown apparently swollen mitochondria with poorly defined cristae, the mPT pore persistently opening and the reduced ΔΨm compared with the sham group. Importantly, the intracellular ATP levels were apparently decreased to 17.6 ± 7.9% of normal condition, although treatment of reinfusion was taken [1-3]. The above changes of morphology (ultrastructure), metabolic (mPT pore and ΔΨm) and function (ATP content) indicated the presence of ASMC mitochondrial damage or mitochondrial dysfunction during hemorrhagic shock. Moreover, expression of histone deacetylase SIRT1, SIRT3 (Fig. 2), proliferator-activated receptor coactivator-1α (PGC-1α) and respiratory protein (such as COX IV), were decreased in parallel, as well as oxygen consumption and ATP production [2]. SIRT1 and mitochondrial SIRT3 emerged as crucial regulators of mitochondrial biogenesis and function [25]. PGC-1α is a co-activator of transcription, which promotes the expression of nuclear-encoded mitochondrial genes involved in mitochondrial biogenesis and/or function [26, 27]. SIRT1 can activate PGC-1α to increase mitochondrial fatty acid oxidation in the muscle, and improve running performance, muscle strength and coordination [28]. We found that decreased expression and activity of SIRT1/3 deacetylase promoted persistent opening of mPT pore and mitochondrial injury in mesenteric ASMCs in severe shock [2]. Moreover, the activation of SIRT1/3 by Res or SRT1720 restored SIRT1/3 activity and protein expression and suppressed mitochondrial injury (Fig. 3) [2]. Importantly, at 2 h post-bleeding, the administration of SIRT1 activator improved vasoresponsiveness to noradrenaline and refractory hypotension during hemorrhagic shock in vivo (Fig. 4) [2]. With this line of reasoning, mitochondrial biogenesis reprogramming is responsible for refractory hypotension.
Figure 2. SIRT1/3 expression and activity are down-regulated in ASMCs during hemorrhagic shock. A. SIRT1/3 protein expression and activities are reduced in ASMCs following severe shock. Representative immunoblots of 6 separated experiments and quantitative analysis showed that the expression of SIRT1 and SIRT3 was decreased in ASMCs. B. Deacetylase activities of SIRT1 and SIRT3 are decreased in ASMCs during severe shock. C. Representative immunofluorescence staining images show that SIRT1 is located in the nucleus of ASMCs but nuclear localization of SIRT1 is decreased following severe shock. The localization of SIRT3 in the mitochondria is decreased following severe shock. Scale bar = 10 μm. n=6 or 7; *P < 0.05 vs. sham group. Hs=hemorrhagic shock; Re=resuscitation.
Figure 3. Activation of SIRT1/3 suppresses mitochondrial injury. A. The shock-associated reduction of deacetylase activity of SIRT1 and SIRT3, as assessed by a commercially available fluorometric assay, is inhibited by resveratrol (Res) and SRT1720, a potent SIRT1 activator. EX 527, a selective SIRT1 inhibitor, inhibits the effects of Res and SRT1720. B. Activation of SIRT1/3 by resveratrol (Res) and SRT1720 suppresses the shock-associated mitochondrial injury and decrease in ATP production. Inhibition of SIRT1/3 activity enhances mitochondrial phenotype and functional damage. n = 4; *P < 0.05 vs. sham group; #P < 0.05 vs. shock group; ΔP < 0.05 in shock + Res group or shock + SRT1720 group vs. shock + Ex + Res group or shock+Ex+SRT1720 group.
Figure 4. Activation of SIRT1/3 improves vasoreactivity and mean arterial pressure in the rats during severe hemorrhagic shock. Vasoreactivity and mean arterial pressure were measured before bleeding and at the end of a period including 2 h post-hemorrhage with or without different treatments. A. Activation of SIRT1/3 by resveratrol (Res) and SRT1720 restores low vasoreactivity and improves the hypotension following severe shock. B. Inhibition of SIRT1/3 activity relieves hypotension during severe shock. n = 5 or 6; *P < 0.05 vs. sham group; #P <0.05 vs. shock group; ΔP < 0.05, shock + Res group vs. shock + EX527 + Res group; shock + SRT1720 group vs. shock + EX527 + SRT1720 group.
3. Mitochondrial biogenesis reprogramming in multi-organ dysfunction

Mitochondrial biogenesis and dysfunction and the resultant cytopathic hypoxia per se serve as a key in the pathogenesis of multi-organ dysfunction. In the heart, it is demonstrated that Myc activation stimulates mitochondrial biogenesis by reducing PGC-1α levels in the myocardium of adult mice and plays important roles in attenuation of ischemia-induced cardiac dysfunction and infarct size [29]. In the liver, hexokinase III (HKIII), an important enzyme in glucose metabolism, was found to reduce oxidant-induced ROS production, preserve mitochondrial membrane potential, increase ATP levels and increase mitochondrial biogenesis, resulting in cytoprotection after hypoxia [30]. In a model of oxidative injury mimicking ischemia-reperfusion renal damage, PGC-1α-mediated mitochondrial biogenesis accelerated recovery of mitochondrial function in the renal proximal tubule, provided a promising target to accelerate recovery of cellular functions and may have important implications in the treatment of acute renal failure and other epithelial injuries [31]. In ischemic neurons, LPS preconditioning increased the expression of critical components of the mitochondrial transcriptional machinery, including nuclear respiratory factor 1 and mitochondria transcription factor A (TFAM), as well as mtDNA copy number, mitochondrial protein levels and markers of functional mitochondria, such as increased cellular ATP content, citrate synthase activity and maximal respiration capacity [32]. Induction of mitochondrial biogenesis is highly correlated with and serves as a critical mediator in LPS-induced ischemic neuron tolerance [32].

In addition to arterioles, we have also demonstrated the mitochondrial injury in neurons, hepatocytes, small intestine and renal tubular epithelial cells during severe hemorrhagic shock. The most common change in multiple organs observed under hemorrhagic shock is cellular stress accompanied by alterations in energy metabolism initiated at the mitochondria. It was found that a series of markers (mPT pore, ΔΨm and ATP) indicating mitochondrial dysfunction were concomitantly depressed. And mitochondrial swelling and crista disappearance even existed at different levels in almost all of the important organs [2, 3, 5, 6]. Interestingly, activation of SIRT1/3 restores mitochondrial function and thus alleviates hemorrhagic shock injury in hepatocytes, small intestine and renal tubular epithelial cells [2, 5, 6]. SIRT1 is the master regulator of mitochondrial biogenesis [25, 33]. Future studies should further verify the
role of mitochondrial biogenesis reprogramming in multi-organ dysfunction during hemorrhagic shock.

4. Epigenetic mechanism in mitochondrial injury

In this section, we highlight recent studies that have uncovered the genes and mechanisms that regulate mitochondrial biogenesis and function. Mitochondrial biogenesis and function is associated with a mitochondrial damage checkpoint (mitocheckpoint) [34]. Upon cellular environmental stimulation or damage to mitochondria, mitocheckpoint modulates crosstalk between the nucleus and mitochondria, which epigenetically alter mtDNA or gDNA expression, leading to mitochondrial damage response [34]. However, despite the well-recognized link between mitochondrial biogenesis and cell stress, the factors regulating mitochondrial biogenesis have remained elusive.

4.1. Acetylation and deacetylation

Histone acetylation is one of the best-studied forms of chromatin modification and is associated with transcriptional activation [35]. Acetylation and deacetylation requires specific metabolic coenzymes whose biosynthesis depends on intracellular ATP levels and mitochondrial function [35]. Conversely, histone acetylation is involved in regulation of mitochondrial respiration and mitochondrial function [35]. A large number of studies have highlighted the crucial role of SIRTs, NAD$^+$-dependent protein deacetylases, in the control of the cellular energy status and in the regulation of metabolism, stress responses, and aging [2, 19, 36, 37]. It is evident that mitochondrial biogenesis is regulated at least in part by PGC-1α as well as other transcription factors [38]. PGC-1α is a deacetylation target of SIRT1, which regulates PGC-1α activity in liver and skeletal muscle [39, 40]. The SIRT1-dependent deacetylation of PGC-1α is required for mitochondrial biogenesis in liver and skeletal muscle [39, 40]. Recently, our laboratory contributed to unravel the role of SIRT1 in mitochondrial biogenesis and function. Indeed, we observed that SIRT1 interacts with SIRT3, the mitochondrial sirtuin, mediates deacetylation of CyPD, an important mPT pore component, and then regulates mPT pore opening and mitochondrial function in rat ASMCs during hemorrhagic shock (Fig. 5) [2]. To support these evidences, treatment of rats with SRT1720 and resveratrol, SIRT1 activators, suppressed mPT pore opening
Figure 5. MPT pore opening is associated with acetylation of CyPD in ASMCs during hemorrhagic shock. **A.** Representative immunofluorescence staining images show that acetylation of CyPD (white) is increased in ASMCs following severe shock. **B.** MPT pore alterations during severe shock are analyzed by staining the cells with calcein-AM/CoCl2. A shift of the curves to the left indicates progressive decrease in the mean fluorescence intensity (MFI) of calcein. MFI of calcein is decreased especially at the time points of 10 min and 120 min after resuscitation in severe shock, suggesting the opening of mPT pore at the onset of resuscitation. Scale bar = 10 μm. N = 6 or 7; *P < 0.05 vs. sham group. Hs = hemorrhagic shock; Re = resuscitation.
and ameliorated mitochondrial injury and its associated vascular hyporeactivity [2]. In another study, we found that the expression and activity of SIRT1 are decreased in pulmonary arteriolar smooth muscle cells (PASMCs) exposed to hypoxia and reoxygenation. PGC-1α/SIRT3/CyPD mediates the effect of SIRT1 on TFAM and mtDNA expression in mitochondria, which regulates PASMC mitochondrial biogenesis and function [19]. Hence, acetylation and deacetylation may play important role in mitochondrial biogenesis reprogramming in ischemia/reperfusion or hemorrhagic shock.

4.2. Methylation

The mtDNA is mitochondrial owned independent genome. Mammalian mtDNA encodes 37 genes: two ribosomal RNAs, 22 transfer RNAs, and 13 proteins that are part of the mitochondrial OXPHOS complexes [41]. mtDNA has ~440 CpG sites. Methylation of mtDNA can regulate mitochondria copy numbers and is associated with aging and chronic diseases, including amyotrophic lateral sclerosis, diabetes and cancer [42, 43]. DNA methyltransferase (Dnmt) 1, the major enzyme, is responsible for maintenance of DNA methylation and also has a mitochondrial targeting sequence. Mitochondrial D-loop methylation in colorectal cancer is associated with altered expression of mtDNA-encoded NADH dehydrogenase 2 of complex I [44]. In diabetes, the activity of retinal Dnmt is increased, which mediates hypermethylation of mtDNA replication enzyme, polymerase γ-1, and impairment of its binding at the D-loop, leading to decreased mitochondrial biogenesis [43, 45]. It was demonstrated that patients with cardiovascular diseases showed higher methylation levels than healthy individuals in several mitochondrial genes in platelets [46]. mtDNA methylation status has been proposed as a new biomarker for the detection and diagnosis of diseases, indicating that mtDNA methylation may be involved in the onset or progression of pathological conditions [46]. However, hemorrhagic shock affected mtDNA methylation and the role of mtDNA methylation in mitochondrial biogenesis and function remains to be elucidated.

4.3. MicroRNAs and long noncoding RNAs

MicroRNAs (miRNAs) are approximately 21-23 nucleotides small RNA molecules, which are emerged as new epigenetic regulators of gene expression [47]. miRNAs can target mitochondria to affect mitochondrial biogenesis and mitochondria to produce ATP. miR-15b, miR-16, miR-195,
and miR-424 have been reported to reduce ATP levels in neonatal cardiac myocytes by targeting the ADP-ribosylation factor-like 2 [48]. miR-423-3p modulates the ATP level partly by regulating the expression of mitochondrial energy metabolism genes including cytochrome C oxidase subunit 6A2, complex I-B18 and NDUFS5 (NADH:Ubiquinone oxidoreductase subunit S5) in C2C12 murine myoblasts [49]. miR-27b activates ATP synthase ATP5A1 and reactive oxygen species-detoxifying enzymes superoxide dismutase 3, glutathione peroxidases 3 and 4 and uncoupling protein 2 in a PGC-1α-dependent manner, leading to increase in ATP production and mitochondrial biogenesis in adipose-derived mesenchymal stem cells [50]. In skeletal muscles from HFD-fed obese mice, miR-149 inhibits poly(ADP-ribose) polymerase-2 and increased cellular NAD+ levels that subsequently enhances mitochondrial function and biogenesis via activation of the SIRT-1/PGC-1α pathway [51]. Particularly, mitochondrial-located miR181c has been demonstrated to regulate a mitochondrial gene, cytochrome c oxidase subunit I, alter O2-consumption, mitochondrial calcium and mitochondrial ΔΨm, increase production of ROS, and affect mitochondrial function in cardiomyocytes in vivo, leading to cardiac dysfunction [52, 53].

Long noncoding RNAs (lncRNAs) have a transcript length longer than 200 nucleotides and play a crucial role in the regulation of epigenetic processes, e.g., RNA splicing and genomic imprinting or as enhancers in cell differentiation [54]. Recent evidence indicates that lncRNAs may contribute to the synchronization of a series of essential cellular and mitochondrial biological processes, acting as “messengers” between the nucleus and the mitochondria [55]. Some mitochondrial lncRNAs such as LIPCAR, uc004cov.4 and uc022bqu.1 have been verified as a blood based biomarker for cardiac remodeling after myocardial infarction in chronic heart failure and in patients with hypertrophic cardiomyopathy [56, 57]. In the heart, several lncRNAs (CARL, MDRL, AK048451 and APF) were shown to act as the sponge of miRNAs (miR-539, miR-361, miR-489 and miR-188-3p) and epigenetic regulators to inhibit mitochondrial fission and apoptosis, resulting in controlling ischemia-reperfusion injury [58-60]. However, the role of miRNAs and long noncoding RNAs for the mechanism underlying hemorrhagic shock remains largely unexplored.

### 4.4. Mitochondria based therapeutic approaches

Some clinical trials and a larger number of experimental investigations have reported pharmacological and nutritional management strategies improve mitochondrial activity and resultanty develop positive effects on
pathological conditions. Although preliminary, the results point to the need of further research. There are increasing evidences that strongly implicate a role of mitochondrial dysfunction in the pathogenesis of hemorrhagic shock and multi-organ dysfunction. Our previous study demonstrated that mitochondrial injury in vascular cells leads to the impaired vasoreactivity and microcirculation during hemorrhagic shock [1-3]. Polydatin is a glucoside of resveratrol, a natural polyphenolic compound. Polydatin protects multiple organs from ischemia/reperfusion injury [61-63]. Importantly, we found polydatin protects against ASMC mitochondrial injury in hemorrhagic

**Figure 6.** Polydatin improves mitochondrial biogenetic reprogramming and mitochondrial function through activation of SIRT1 in PASMCs exposed to HR. A. Polydatin restored the expression of SIRT1 in PASMCs exposed to HR. SIRT1 siRNA knocked down the expression of SIRT1. Knockdown of SIRT1 suppressed the protective effect of polydatin on mtDNA content during HR. B. Polydatin increased the expression of TFAM in PASMC mitochondria during HR. Knockdown of SIRT1 suppressed the effect of polydatin. C. Polydatin increased ATP levels in PASMCs during HR. Knockdown of SIRT1 suppressed the protective effect of polydatin. n = 5 in each group; *P < 0.05 vs. untreated control; #P < 0.05 vs. HR; †P < 0.05 vs. lenti-SIRT1+HR or lenti-control+HR. HR, hypoxia-reoxygenation.
Mitochondrial biogenesis reprogramming in shock [64]. We also found resveratrol and SRT1720 activate SIRT1/SIRT3 to prevent persistent opening of mPT pore and protect mitochondrial function, leading to improving microcirculation, MAP and survival after severe hemorrhagic shock [2]. Recently, we found polydatin protects mitochondria through activation of SIRT1 in liver, small intestine and kidney during hemorrhagic shock [4-6] and protects against mitochondrial biogenesis reprogramming and function in PASMCs during hypoxia-reoxygenation (Fig. 6) [19].

Presently, there are some studies reporting potential therapeutic mitochondrial targets of miRNAs and lncRNA for treatment of cardiovascular diseases. MiR-181c delivered to the heart in vivo can targets mt-COX1 in the mitochondria and protect mitochondrial function, resulting in decreased infarct size in miR-181c/d~m~ mice [53]. LncRNA CARL acts as a sponge for miR-539 and negatively regulates miR-539 expression, leading to suppression of mitochondrial fission and cardiomyocyte apoptosis [58]. There is certainly a growing body of data verifying that mitochondrial dysfunction occurs not only in experimental models but also in critical care patients. Current therapeutic options include antioxidant therapy, nitric oxide donors, and low-level laser therapy, which modulate mitochondrial biogenesis and function, but further studies are necessary to clarify possible benefits for critical care patients [65]. Therefore, mitochondria may serve as, or are linked to, potential targets for the prevention, diagnosis, and treatment of human diseases. Although the clinical application of mitochondria-based biomarkers and therapies is perhaps premature, the rate of discovery is promising. Further studies are needed to provide new insights for the development of specific and effective mitochondria-based therapeutic approaches for treatment of refractory hypotension and multi-organ dysfunction during hemorrhagic shock and other human diseases.

**Summary and conclusions**

Our review highlights that the significance of mitochondrial biogenesis reprogramming in refractory hypotension and multi-organ dysfunction during hemorrhagic shock. Epigenetic modifications play important role in mitochondrial biogenesis reprogramming in numerous ways. These novel findings indicate that mitochondria are a promising therapeutic target for refractory hypotension following severe shock and other diseases connected with cytopathic hypoxia. We are only beginning to understand the full complexity of this regulation. The demonstration of the crosstalk between epigenetic mechanisms and mitochondrial biogenesis reprogramming will open the path to interventions by which mitochondria could be manipulated...
as a potential strategy for detection and treatment of refractory hypotension and multi-organ dysfunction during hemorrhagic shock.

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References

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