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Cardiac Function and Organ Blood Flow at Early Stage Following Severe Burn

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1. Introduction

Multiple organ dysfunction syndrome (MODS) has been the difficulty in clinical treatment of severe burns. In the 1990s, the incidence rate of MODS was 28.1% in severe burn patients, while the mortality rate was as high as 78%-98% (Huang et al., 1998). MODS was caused by two "attacks": the first attack was the early plasma leakage and the effective circulating blood volume reduction, as resulted in the systemic hypoxic-ischemic damage; the second attack was the invasion of consequent systemic inflammatory response and sepsis on the organs (Sheng, 2002). With enhancement of the clinical treatment of burns, the present point of view argues that the key to prevention of MODS is against the first "attack", ie, to control the burn shock, which can effectively prevent or mitigate the second "attack" to reduce the incidence of MODS (Sheng, 2002).

Previously, only hypovolemia was concerned in the patients with burn shock. However, it is found that simple increase of the blood volume can not effectively curb the incidence of burn shock in a large number of clinical treatments of severely burned patients. These group of patients are often accompanied by hypodynamic blood circulation, thus too much or fast fluid perfusion may easily induce heart failure. Therefore, we have shifted our attention to the heart, a motivator organ for blood circulation. We further found that the heart is not the sole organ injured early by serious burn, and this damage and reduced pump function occurred before the vascular permeability change and the blood volume decrease (Huang, Li, & Yang, 2003; Huang et al., 1999b). The immediate early myocardial damage and weakened pump function of the heart can not only cause heart failure, but also induce or aggravate shock and hence become one of the generators leading to severe burn shock and systematic hypoxic-ischemic damage. Based on above, we proposed the hypothesis of "shock heart" involving systematic hypoxic-ischemic damage early after burn injury (Huang, Zheng, Fan, & Zhang, 2007; Huang, 2009; Xiao et al., 2008b). In order to confirm this hypothesis, we have conducted a large number of animal experiments and clinical trials. On the one hand, we explored the effects of the early emergence of myocardial damage and cardiac dysfunction on the systemic organ perfusion and hypoxic-ischemic injury; on the other hand, an in depth study has been done on its development mechanism so as to find effective therapeutic targets for clinical use.

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2. Early changes of cardiac function after severe burns

In the early 1960s, Fozzard observed myocardial damage and cardiac output decrease in the burn patients and further found that this kind of heart failure was not due to pre-injury heart disease or excessive fluid infusion (Fozzard, 1961). Some scholars attributed the cardiac dysfunction to the vascular leakage of plasma into the injured area, causing decreased venous return and cardiac preload reduction (Evans, Purnell, Robinett, Batchelor, & Martin, 1952). Nonetheless, the subsequent experimental results differed from this view. The researchers found that before obvious extravasation of plasma, the cardiac output was significantly reduced and even a large volume of fluid resuscitation could not improve the cardiac output . (Moyer, Coller, Iob, Vaughan, & Marty, 1944) Therefore, it was considered that the microcirculatory disturbances, abnormal coagulation system (Brooks, Dragstedt, Warner, & Knisely, 1950) and peripheral vasoconstriction (Salzberg & Evans, 1950; Wolfe & Miller, 1976) after severe burn were key causes to the combined cardiac dysfunction. In 1984, Adams et al established a guinea pig burn model to study the systolic and diastolic function changes of the the left ventricle after the injury. They found that when the burn injury exceeded 47% of the total body surface area (TBSA), the ventricular compliance was reduced and the cardiac isovolumic relaxation period extended, accompanied by significant myocardial contractile dysfunction, based on which they viewed that inherent myocardial damage led to the decrease of the adverse cardiac filling and ejection fraction of the left ventricle (Adams, Baxter, & Izenberg, 1984).

Cardiac dysfunction after severe burns has been confirmed in many experimental studies. However, the myocardial systolic/diastolic dysfunction occurred in different time post-burn in different species animal models including mice, rats, hamsters, guinea pigs, rabbits, dogs, pigs and sheep (Adams, Baxter, & Parker, 1982; Baxter, Cook, & Shires, 1966; Elgjo et al., 1998; Ferrara et al., 1998; Fozzard, 1961; Horton, Garcia, White, & Keffer, 1995; Horton, Maass, White, Sanders, & Murphy, 2004; Horton, White, Maass, & Sanders, 1998; White, Maass, Giroir, & Horton, 2001). Horton et al studied time course of heart function of the rabbit and rat after burn by dissecting the heart for in vitro perfusion at each time point. The results showed a transient decrease of the cardiac function after burn, which first appeared at 2 hours, decreased continually within 24-30 hours and gradually recovered at 48-72 hours after burn injury (Horton et al., 1995; Maass, Hybki, White, & Horton, 2002; Sheeran et al., 1998). This short-term decreased heart function may be less risk for the otherwise healthy young adults with burn but may be so risky for the young, the elderly and the immunocompromised patients that they had to receive unaffordable fluid resuscitation. Recent studies also showed that the cardiac dysfunction after burn is an index for predicting the proneness to secondary infection, ie, it is closely related with morbidity and mortality of MODS in severely burned patients and can predict the long-term infection complications.

Over the past 10 years, our laboratory have carried out a series of burn research on the pig, dog, rabbit, rat and other animal models and particularly established a mature rat model with 30% TBSA 3rd degree burn. When the rats were under anesthesia, the cardiac function was detected by inserting the catheter from the carotid artery to the left ventricle, when the other end of the catheter was connected with pressure transducer and multi-channel physiological recorder. Number of myocardial mechanical indicators were recorded early after burn injury (24 hours) at several preset time points, which could help deeper understand the course of the cardiac function change in the early time after burns (Xiao, Lei,

Dang, & Huang, 2011). As shown in Figure 1, in rats with 30% TBSA 3rd degree scald injury, the maximal rate of the rise/drop of left ventricular pressure ($\pm$ dp/dt max) was significantly reduced 1 hour post-burn, while the mean arterial pressure (MAP) was declined until 3 hours after injury, indicating that the cardiovascular system itself has a certain compensatory ability and a stable blood pressure can be maintained temporarily by increasing the peripheral resistance. Our results showed that the heart function reached a valley at 12 hours after burn injury, then recovered for some extent but still remained at a low level at 24 hours after injury, which differed from the aforementioned time course results (the valley emerged at 24-30 hours after injury) reported by Horton et al. This difference may be due to different cardiac function test methods, ie, in vitro heart perfusion and in vivo intubation. However, our results undoubtedly confirm that the cardiac function was weakened rapidly after burn (1-2 hours after injury), when there was no obvious plasma extravasation or reduction of effective circulating blood volume (Carvajal, Linares, & Brouhard, 1979; Salzberg & Evans, 1950). Therefore, we can be sure that the cardiac dysfunction soon after severe burns was caused by myocardial cell damage and myocardial systolic/diastolic dysfunction of the heart itself rather than the burn shock, as is worthy of further study and exploration on these endogenous mechanism.
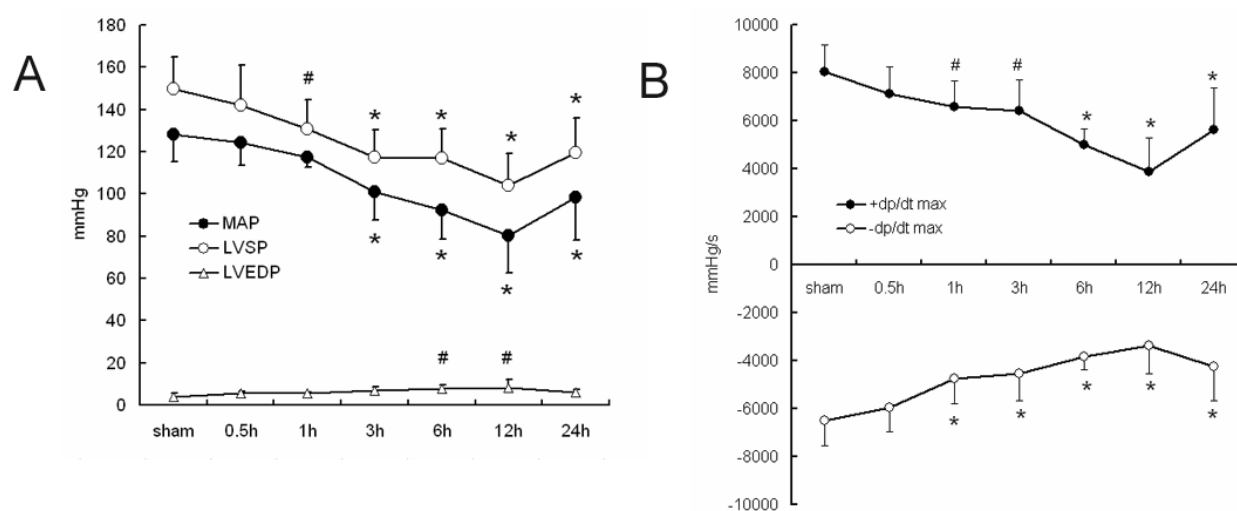

Fig. 1. Time course of heart function after 30%TBSA 3rd degree burns in rats in vivo. All values are mean ± SEM. MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; ± dp/dt max, maximal rate of the rise/drop of left ventricular pressure. * p<0.05 vs sham.

3. Organ perfusion at early stage following severe burns

Severe burns induce a strong stress response and high excitement of the sympathetic-adrenal medulla system. The catecholamines secreted by the sympathetic-adrenal medulla system can adjust the heart excitement, the peripheral vascular resistance and the capacitance vessels so that the blood supply to tissues and organs at the shock stage becomes more adequate and reasonable. However, the anatomy, physiology and tolerance to ischemia and compensatory ability differs in various organs, which leads to different blood supply of the main organs including heart, brain, liver, kidney and intestine after severe burns.

3.1 Heart

The traditional pathophysiological view was that under severe stress conditions, especially reduction of the effective circulating blood volume, the body reduced the blood supply of most abdominal organs and gave priority to ensuring the blood supply of the heart, brain and other vital organs. However, a lot of experiments conducted in our laboratory confirmed no effective protection of the myocardial blood supply after severe burns. Early in 1996, Yang et al (Yang, Yang, & Chen, 1996) used radioactive tracer ^{86}Rb uptake to detect the myocardial nutritional blood flow (NBF) changes of rats with 30% TBSA 3rd degree burn (Figure 2). The results showed that the myocardial nutritional blood flow was reduced by about 24% 1 hour after burn, then continued to decrease up to the valley at 12 hours and recovered mildly at 24 hours (but still lower than the sham group), which was similar to the trend of cardiac function change. Moreover, the earliest time point for determination of the myocardial blood flow was at 1 hour after injury, which was the same time that the cardiac function began to decline. Nonetheless, we are not sure about whether the myocardial ischemia damage resulted in decreased heart function or the reduced cardiac output led to the coronary flow decrease. Therefore, the myocardial blood flow was detected in the rats with 30% TBSA 3rd degree burns by using the fluorescent microspheres method at 10 min, 30 min, 1 hour, 3 hours and 6 hours post-burn (Figure 3). The results showed that the regional myocardial blood flow was decreased significantly at 10 minutes, recovered mildly at 30 minutes and 1 hour, and then continued to decline after burn (Yin, Huang, & Li, 2010). The myocardial blood flow was rapidly reduced 10 minutes after burn, which may be related to the contraction of the coronary caused by myocardial renin-angiotensin system (RAS) that was activated immediately after burn (Mackins et al., 2006). We used the enzyme linked immunosorbent assay (ELISA) method to detect the Ang II in the myocardial (Figure 4) and the results showed that the myocardial Ang II was increased from 10 minutes after injury. This is a very good explanation of the transient reduction of the myocardial blood flow at 10 minutes after burn. The subsequent rebound increase of the blood perfusion may be due to accumulation of hypoxic metabolites that offset or exceeded the vascular contraction effect of Ang II and finally caused vasodilation.
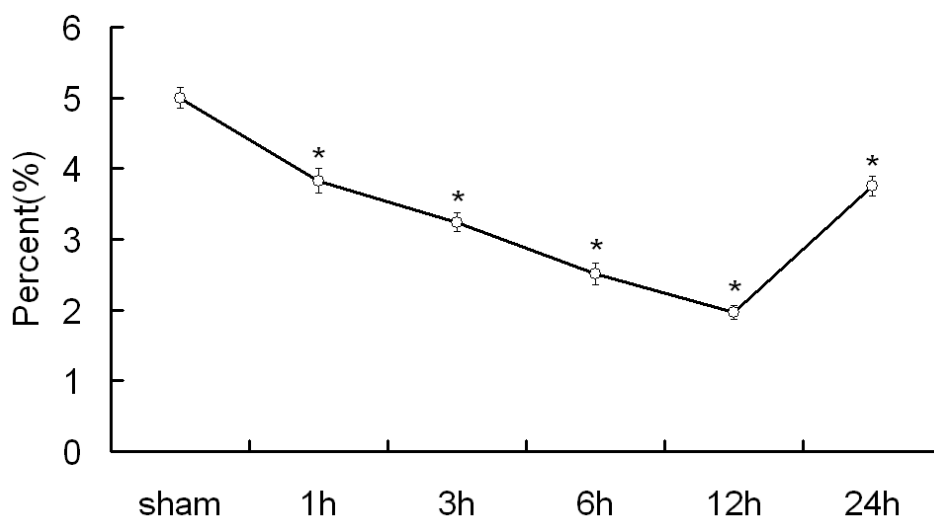

Fig. 2. Myocardial nutrition blood flow of the rats following 30%TBSA 3rd degree burns. All values are mean ± SEM. * p<0.05 vs sham.
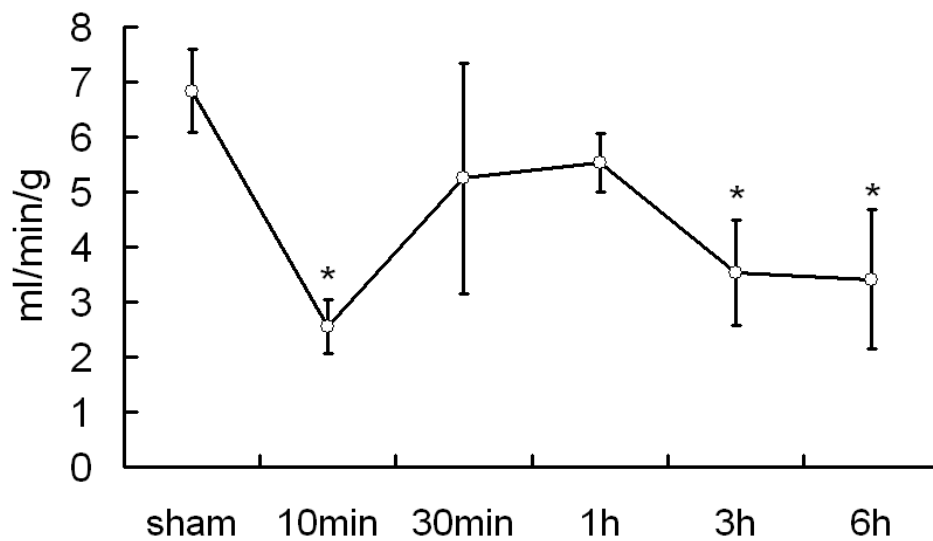
Fig. 3. Myocardial blood perfusion of the rats following 30%TBSA 3rd degree burns. All values are mean ± SEM. * p<0.05 vs sham.

In fact, under continuous increase of the Ang II, the compensatory mechanism of the heart itself was difficult to maintain too long and turned into decompensation about 3 hours post-burn, with continual decrease of the myocardial blood flow. Thus, the myocardial blood flow was reduced before cardiac dysfunction after severe burns, indicating that the myocardial ischemia and hypoxia was the main cause for the cardiac dysfunction (Huang et al., 2003).
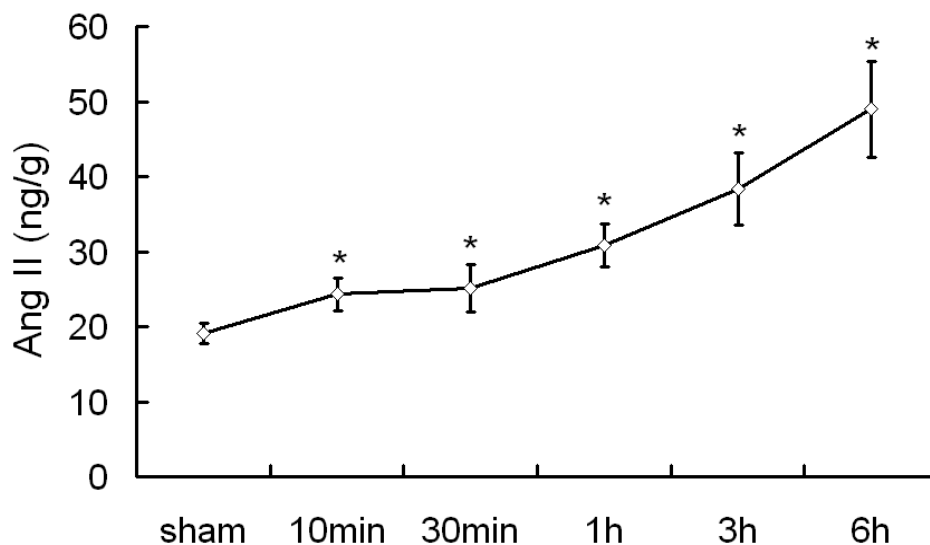

Fig. 4. Content of cardiac local angiotensin II in the rats following 30%TBSA 3rd degree burns. All values are mean ± SEM. * p<0.05 vs sham.

3.2 Brain

Currently, there has seldom reported the cerebral blood flow perfusion at early stage after severe burns. But the cerebral edema was often complicated clinically after burn, the

pathological factors for which was different from brain trauma or brain damage simply caused by brain trauma or hypoxia. The complicated cerebral edema after burn is due to destructed microcirculation and blood-brain barrier function as well as increased permeability resulted from a variety of factors including ischemia and hypoxia, cell medium, endotoxin, electrolyte imbalance, acidosis and uncontrolled inflammation, which ultimately caused diffuse tissue edema. The vascular endothelial cells played a key role in the pathogenesis of brain edema after burn. On the one hand, the vascular endothelial cells had clear morphological changes, even formation of cracks and endothelial cell loss leading to the semi-permeable membrane barrier dysfunction and vascular permeability increase. On the other hand, the vascular endothelial cells could release a variety of media to further promote the microcirculation disorder, aggravate tissue ischemia and hypoxia and promote development of the tissue edema (Domres, Heller, & von Kothen, 1981; Li et al., 2001).
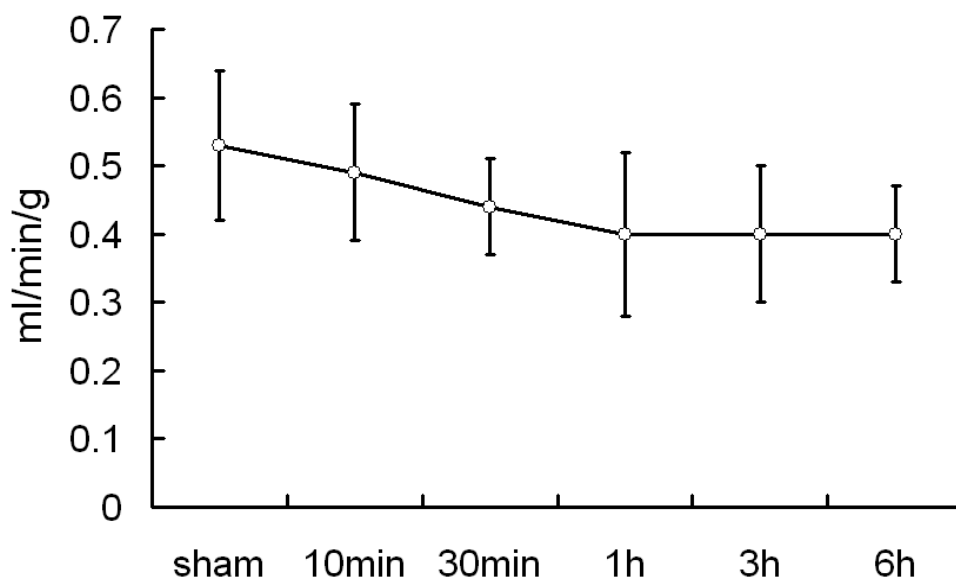

Fig. 5. Cerebullar blood perfusion of the rats following 30%TBSA 3rd degree burns. All values are mean ± SEM.

We have used the same fluorescent microspheres method to detect the brain blood flow in rats with 30% TBSA 3rd degree burns (Figure 5), which showed insignificant statistical difference upon the cerebral blood flow at all time points, indicating that the brain tissues still had a strong compensatory ability even after burn injury. Because the brain tissue has the minimum tolerance to the hypoxia out of all organs, the brain blood supply can still remain stable unless under a serious shortage of blood volume.

3.3 Reduced perfusion and hypoxic-ischemic injury of the liver, kidney and intestine

Catecholamines in the blood at early stage after burn was increased tens even hundreds times more than that in the normal time. The small blood vessels in the abdominal organs and kidney had rich sympathetic vasoconstrictor innervation, with dominant α-adrenergic receptors. With sympathetic excitement and catecholamine increase, the microvascular contraction of these organs significantly increased precapillary resistance and sharply decreased the microcirculation perfusion. While the β-adrenergic receptor stimulation

opened the arterial-venous anastomosis, which resulted in increase of the microcirculation non-nutritive blood flow, decrease of the nutritional blood flow and severe tissue ischemia and hypoxia. In addition, a great deal of Ang II produced by the activated circulatory system RAS was also involved in the vasoconstriction (Dolecek, Zavada, Adamkova, & Leikep, 1973).

The laser Doppler flowmetry was employed to detect the blood flow of liver, kidney, and intestines of the rats with 30% 3rd degree burns, which showed that the hepatic, renal, and intestinal perfusion was significantly declined 1 hour post-burn and recovered for some extent at 24 hours (Figure 6). The blood flow changes differed significantly in different organs, ie, the blood flow was reduced the most significantly in the kidney, followed by the intestine and the liver the least. Despite obvious decrease, the hepatic blood flow remained stable overall. Judging from the recovery, the liver restored the blood flow better at 24 hours after burn, while the kidney and intestinal ischemia were still under serious condition, especially the intestines, which may be due to so-called "covert compensated shock", ie, the blood supply was difficult to recover even quite a long time after adequate systemic blood supply (Fiddian-Green, Haglund, Gutierrez, & Shoemaker, 1993).
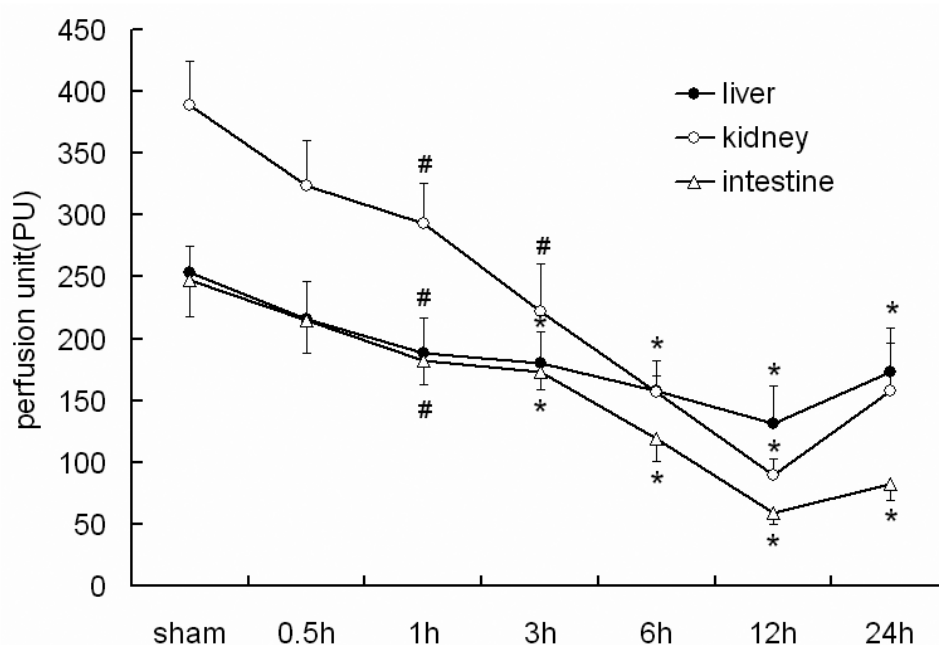

Fig. 6. Blood flow to liver, kidney, and intestine in the rats following 30%TBSA 3rd degree burns. All values are mean ± SEM. * p<0.05 vs sham.

Liver blood supply has its own peculiarities, the portal vein and hepatic artery converged in to the hepatic capillary network and subsequently returned to heat via the hepatic vein. Under the resting state, 20% of the cardiac output entered into the liver, of which 1/3 passed by the hepatic artery and 2/3 by the portal vein. Liver cells are extremely sensitive to the ischemia and hypoxia, easy inducing the liver cell damage. The central lobular hepatocytes received less blood flow than the peripheral cells of the lobule and it suffered the earliest and the most serious damage. Visceral injury was closely related to the circulatory state especially the micro-circulation after burn. After the ischemic phase, the substrate

concentration of the intracellular xanthine oxidase was increased, which prompted the substrate transforming to the xanthine oxidase via proteolysis or histamine. During the course of reperfusion, a large number of free radicals were produced with the improvement of hypoxia and finally induced reperfusion injury (Horton, 2003). Toklu et al detected malondialdehyde (MDA), reduced glutathione (GSH) level and myeloperoxidase (MPO) activity of skin, lung, liver, ileum and kidneys in rats at 6 and 48 hours after burns and found significant increase of MDA level and MPO activity but decrease of antioxidant GSH content; hence they viewed that the oxygen free radicals and lipid peroxidation plays an important role in organ damage after burn injury (Toklu et al., 2006). Sakarcan et al carried out similar experiments to confirm the protective effect of antioxidant Ginkgo biloba extract (Egb) on the rat organs after burn injury and the results showed increase of MDA level and MPO activity but decrease of GSH in the liver and kidney, together with increase of AST, ALT, BUN, Cr and LDH, as suggested liver and kidney dysfunction (Sakarcan et al., 2005).

Zhou et al observed a series of liver changes 1 hour after burn in rats, mainly swelling, degeneration and necrosis of the hepatocytes, fatty degeneration or eosinophils detected by the light microscope, which resulted in point-like or small focal hepatocyte necrosis. In the meantime, the electron microscopy manifested different degrees of ultrastructure change of the hepatocytes and extensive damage to the nucleus and organelles. Their study also showed that ALT was increased at 1 hour and reached the peak at 12 hours after burn and that AST began to increase at 6 hours and continued to 48 hours after burn. The increase of blood AST and ALT was the inevitable result of serious liver parenchyma damage, indicating that burns can cause liver damage and progressive aggravation in a relatively short period of time. Especially the degeneration and necrosis of the hepatocytes, mitochondria degeneration and endoplasmic reticulum will undoubtedly and directly affect the normal function of the hepatocytes and weaken the detoxification function of the burn injury liver, when acute liver failure may occur in a few burn patients (Zhou, Huang, & Chen, 2002).

In the normal adult, the kidney is body organ with the largest blood flow, with 1000-1250ml/min, accounting for 20%-25% of cardiac output. The renal damage at burn shock stage is primarily due to sharp decline of the blood volume, reduction of the cardiac output and decrease of the renal blood flow. The heart failure induced by severe burns would directly result in of the effective circulating blood volume decrease, the sympathetic excitement and the redistribution of systemic blood, which affected the renal blood flow the most, with reduction of glomerular blood flow and filtration to 30%-50% or less of the normal (Figure 6). When the arterial pressure fell below 60 mmHg, the glomerular filtration would even stop and lead to anuria or oliguria. Sener et al found significant decrease of renal tissue GSH, increase of MDA, protein oxidation (PO) level and MPO activity and renal dysfunction (increase of BUN and local LDH) in rats at 6 hours post-burn and they argued that the kidney damage was mainly caused by lipid peroxidation and oxygen free radical damage and that the antioxidants Mesna exerted a protective effect on the kidneys (Sener et al., 2004). For oxygen free radical damage, Sener et al conducted a similar experiment in an attempt to prove the role of melatonin in preventing early kidney injury after burns (Sener, Sehirli, Satiroglu, Keyer-Uysal, & Yegen, 2002).

The nerve-humoral regulation early after burns induced redistribution of the blood and the gastrointestinal hypoperfusion lasted for the longest. The blood flow of intestinal mucosa

and villi accounted for 80% and 60% of total gastrointestinal tract blood flow. A 10% decrease of systemic blood volume may lead to 40% decrease of the whole gastrointestinal tract blood flow. The vascular loop of the intestinal villi was with an extremely bent ring structure, which contributed to a short circuit exchange of the central villus arterioles with the venules and capillaries. Under shock and low perfusion state, the short circuit exchange increased to further reduce the oxygen supply of the villus top. The intestinal tissue had high metabolic rate and demanded great deal of the oxygen, indicating that the intestinal tissue was sensitive to ischemia and hypoxia and easy to be damaged, with slow recovery. Under stress state, the mucosal partial pressure of oxygen was decreased but the lactic acid levels significantly increased, the latter of which, during the ischemia-reperfusion process, released large amounts of oxygen free radicals that were the initiating factor for inflammatory mediators and cytokines cascade (Gianotti, Alexander, Pyles, James, & Babcock, 1993).

The burn resulted in up-regulation of a variety of proteins regulating the stress response, reduction of self-repair ability of the intestinal mucosa by free radical damage, energy metabolism disorder of the intestines, increase of cell apoptosis (Zhang et al., 2002), cytoskeletal damage of the intestinal smooth muscle and gastrointestinal motility disorders (Tong, Wang, & Guo, 2006). Reduction of the synthesis of secretory IgA and apoptosis of the intestinal lymph node cells destructed the intestinal immune barrier (Fan, Xie, Zhou, Chen, & Deng, 2006), which may cause damage to the intestinal bacterial translocation and even endotoxemia. The intestinal ischemia-reperfusion injury caused "waterfall-like" cascade of inflammatory mediators by the way of p38/mitogen activated protein kinase (MAPK) (Gan, Pasricha, & Chen, 2007), as made the intestines as the "source" of systemic inflammatory response syndrome (SIRS). The uncontrolled development of SIRS would inevitably lead to MODS or multiple organ failure (MOF), so Hassoun et al considered the intestines was the initiating organ for post-traumatic MOF (Hassoun et al., 2001). Extensive burns, shock and other factors induced potential intestinal hypotension, intestinal hypoperfusion or recessive intestinal shock that may cause intestinal mucos ischemia and hypoxia, intestinal barrier dysfunction, and intestinal SIRS and MODS, as was called "shock bowel" by some scholars (Tu & Xiao, 2002).

3.4 Effect of cardiac dysfunction on hepatic, renal, and intestinal blood flow

The heart is the power organ of the circulatory system. It still remains unclear whether the perfusion changes of the liver, kidney, intestines and other organs is induced by the weakened heart function after burn injury. In order to verify the effect of cardiac function on the liver, kidney and intestine perfusion after severe burns, we established the rat model with 30% 3rd degree burns and then the cardiac function of the rats was intervened with cedilanid, low-dose angiotensin-converting enzyme inhibitor (ACEI) enalaprilat and high-dose β-blocker propranolol. The cardiac function and the blood flow of liver, kidney and intestines were observed at 6 hours post-burn, which showed that cedilanid and low-dose enalaprilat could effectively enhance the heart function; ACEI action on the cardiac function indicated local RAS activation early after burn; Ang II increased the harmful effects of casoconstrictor on the myocardial (Figure 7A); and high-dose β-blocker propranolol could obviously inhibit the cardiac function. It was found that the liver, kidney and intestinal blood flow was significantly increased accordingly with cardiac function improvement and

decreased with further suppression of the cardiac function (Figure 7B). With aim to clarify the effect of cardiac function changes on perfusion of various organs after burn, an analysis was done on the correlation between the mechanical index ± dp/dt max and the liver, kidney and intestinal blood flow, which showed a positive correlation of liver, kidney and intestinal perfusion with the cardiac function after burn (Table 1). The results indicated that immediate early cardiac dysfunction may be an important initiating factor for secondary ischemia and hypoxia damage of multiple organs after severe burn.
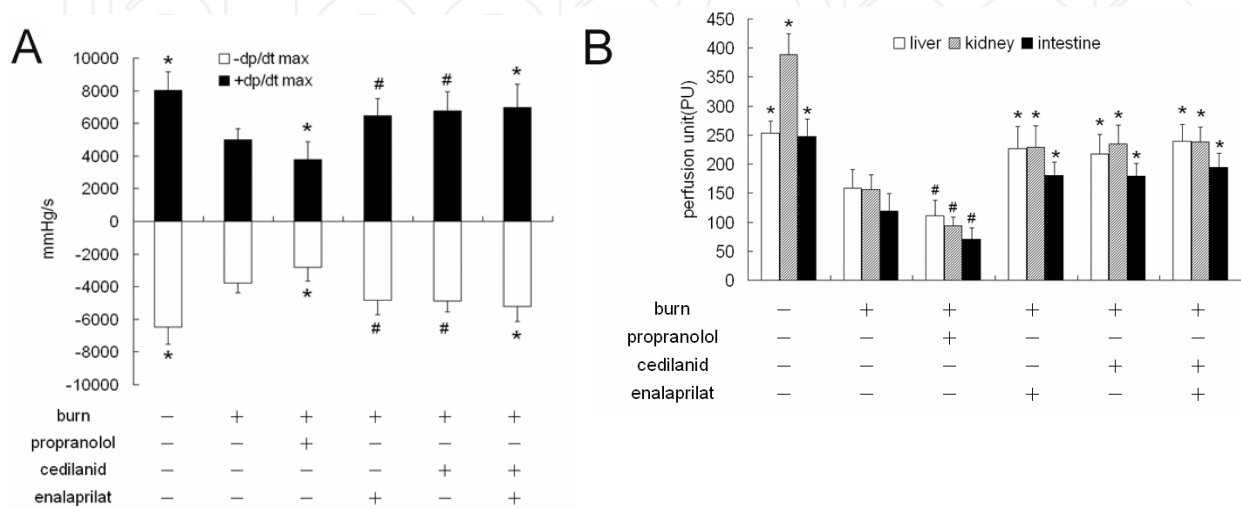

Fig. 7. Cardiac function and blood flow to liver, kidney, and intestine in the 30%TBSA 3rd degree burn rats treated with cedilanid, enalaprilat, and propranolol. All values are mean ± SEM. * p<0.05 vs simple burn.

	+dp/dt max		-dp/dt max	
Parameter tested	†PCC	P value (2-tailed)	PCC	P value (2-tailed)
Hepatic blood flow	0.956*	0.001	0.976*	0.000
Renal blood flow	0.985*	0.000	0.946*	0.001
Intestinal blood flow	0.964*	0.000	0.918*	0.003

Table 1. Summary table of correlation analysis between the maximal left ventricular pressure increase/decrease rate and organ blood flow in rats after a 3rd degree burn. Organ blood perfusion was significantly and positively correlated with heart systolic/diastolic function in rats after the burn (30% of body area) (* P < 0.01). †Pearson correlation coefficient.

4. Mechanism for cardiac damage / heart function depression at early post-burn stage

Undoubtedly, myocardial cell damage is the immediate cause of heart function depression in the early burn period. Back in 1961, Fozzard claimed that myocardial damage may be the reason of cardiac output decrease not matching the change of blood volume (Fozzard, 1961). In the 1990s, serum troponin I (cTnI) was proposed as a highly specific and sensitive indicator in detecting cardiomyocyte injury (Horton et al., 1995). Murphy et al (Murphy,

Horton, Purdue, & Hunt, 1998) randomly examined the level of serum cTnI in a large number of burn patients. They found the serum cTnI was negative in patients with less than 10% TBSA burns, while it continually rose in patients with more than 20% TBSA burns within 12 hours post-burn. It provided solid evidence for post-burn myocardial damage. By testing the serum cTnI in mature rat models of 30% TBSA 3rd degree burns at different time points, we found their serum cTnI levels increased at post-burn 30 minutes, reached the peak at 12 hours, but dropped at 24 hours. Nevertheless, their serum cTnI levels were still lower than the sham (non-burned) group (Xiao et al., 2008a). Bivariate correlation analysis indicated that serum cTnI levels were closely related with the post-burn change in heart function parameters (Xiao et al., 2008a). Other parameters of myocardial damage like myosin light chain 1 (CMLC1) and troponin T (cTnT) also increased evidently after burn (Huang et al., 2003; Huang et al., 1999b). Pathological observation found cloudy swelling of myocardial cells, interstitial vascular dilatation, congestion, edema, hemorrhage and inflammatory cell infiltration at 3 hours post-burn in scalded rats with 30% TBSA 3rd degree burns. At 12h hours post-burn, an irregular arrangement of cardiac muscle fibers (in the wavy-pattern) and sarcoplasm condensation were observed (Zhang et al., 2007a). All these facts implied that cardiac damage already existed in early severe burns, accompanied by decreased heart functions. Then what caused these cardiac damages?

Since the evidence of "burn toxin" presented (Allgower et al., 1968), Baxter and his colleagues attempted to seek myocardial depressant factors (MDF) in the plasma of burn patients. They infused the plasma of burn patients into the free hearts of normal guinea pigs and proved that such plasma was myocardial depressant (Baxter et al., 1966). To avoid species differences and immune reactions, Horton et al collected the serum of 40%TBSA burned rats to infuse the isolated hearts of homogeneous rats. The serum was also proved to be myocardial depressant (Horton et al., 2004). Ferrara et al found that lymph fluid from the posterior limbs of burned animals could reduce the regional myocardial blood flow, resulting in decreased coronary systolic and diastolic activity (Ferrara et al., 1998). Sambol et al found that pre-burn mesenteric lymph duct ligation could greatly improve the impaired cardiac contractile function, which suggested the existence of myocardial depressant factors in burned animals (Sambol, White, Horton, & Deitch, 2002). All these researches implied that burn injuries indeed stimulated the activation and release of certain protein factors which had a negative regulatory or damaging role on cardiac muscles.

Tumor necrosis factor (TNF-α) serum level were initially believed to be associated with the progression of infection (Marano et al., 1990; Marano et al., 1988). Some researchers also thought that the increase of TNF-α in post-burn plasma could be used as a measurement of the body's immune response, which indicated increased risks of secondary sepsis and death (Cannon et al., 1992; Yamada et al., 2000). Subsequent researchers assayed the post-burn TNF-α, IL-1β, IL-6 and other factors and suggested that taking multiple factors into consideration, rather than a single inflammatory factor TNF-α, could better predict the onset of sepsis (Drost et al., 1993a; Drost, Burleson, Cioffi, Mason, & Pruitt, 1993b; Zhang et al., 1998). However, Giroir and Beutler believed that the heart was an important source of TNF-α, although this inflammatory factor could be produced by many other cells and organs (Giroir, Johnson, Brown, Allen, & Beutler, 1992). Then Giroir and Horton studied the role of TNF-α in postburn myocardial dysfunction and found enhanced synthesis of TNF-α by

myocardial cells with a more than 40% TBSA burns. The Anti-TNF-α strategy could prevent myocardial contractile dysfunction and elevate cardiac output (Giroir, Horton, White, McIntyre, & Lin, 1994). Substantial evidence has proved TNF-α to be one of the initial mediators in the "waterfall-like" inflammatory cascade response. In the animal models, intravenous injection of recombinated TNF-α could induce myocardial depression (Eichenholz et al., 1992; Pagani et al., 1992; Tracey et al., 1986). The administration of TNF-α to left ventricular myocardial cells cultured in vitro would produce a concentration-dependent negative inotropic effect (Heard, Perkins, & Fink, 1992; Horton, Maass, White, & Sanders, 2001a; Maass, White, & Horton, 2005; Yokoyama et al., 1993). Meanwhile, the fact that transgenic mice with myocardial overexpression of TNF-α all died of dilated cardiomyopathy and congestive cardiac failure demonstrated its negative effect on myocardial contraction (Bryant et al., 1998). It was also reported that the serum TNF-α increase in the burn patients was not accompanied by signs of infection (Cannon et al., 1992). The level of TNF-α produced by myocardial cells which were isolated from burned rats was 15 times that of the normal control rats (Williams, Bankey, Minei, McIntyre, & Turbeville, 1994). All these facts showed that TNF-α was a significant initiation factor in the postburn uncontrolled inflammatory cascade, as well as an important inflammatory factor in myocardial damage, playing an important role in MODS after sever burns.

In the case of severe burn, tissue ischemia and hypoxic metabolism still continues under large-volume fluid resuscitation (Demling, Ikegami, & Lalonde, 1995). When ischemia is improved in the tissues, re-exposure to molecular oxygen will generate a large number of oxygen free radicals, leading to tissue damage (Horton, 2003). Metabolism of xanthine oxidase (XO) is the major source of oxygen free radicals produced after burns. Allopurinol is a competitive antagonist of XO. Allopurinol-pretreatment can prevent oxyradical-induced myocardial damage and cardiac function depression in rats (Horton & White, 1993). The rise of myocardial lactic acid levels after burns suggests the existence of hypoxic metabolism. Rapid large-volume fluid replacement will remove lactic acid accumulation and improve the myocardial creatine phosphorylation level. The addition of allopurinol to the replacement fluid will remove depolarization in cardiac cell membrane and enhance myocardial contractile function (Horton & White, 1995). Other studies suggested that neutrophil adhesion and activation was another source of oxygen free radicals after burns. Neutrophils release a large number of oxygen free radicals explosively and strengthen the effect of xanthine oxidase, causing damage to tissues and organs (Horton, Mileski, White, & Lipsky, 1996). In addition, burns also destroy the body's antioxidant defense mechanism, so that the tissues are more vulnerable to oxygen free radicals. Further researches found that the rise of MDA in plasma and myocardial tissues led to increase in local concentrations of peroxidized lipid peroxide and conjugated diene. These experiment results all demonstrated the role of oxygen free radicals in postburn organ damage and dysfunction (Cetinkale et al., 1997; Cynober et al., 1985; Demling & LaLonde, 1990a, b; Takeda et al., 1984; Ward, Till, Hatherill, Annesley, & Kunkel, 1985).

Multiple cellular and molecular signal transduction pathways have been verified to cause myocardial damage and mechanical dysfunction. The p38/MAPK pathway, for instance, regulates the synthesis and secretion of cytokines and plays a significant role in many heart diseases like myocardial hypertrophy, ischemia/reperfusion injury, and myocardial cell apoptosis (Sugden & Clerk, 1998; Wang et al., 1998; Zhang et al., 2008b). Myocardial

p38/MAPK activity was evidently elevated in cases of over 40% TBSA burns. This enhanced activity in the early postburn period (at 1 hour, 2 hours, and 4 hours post-burn) could be inhibited by its specific antagonist SB203580. Nevertheless, the activity of JNK was not interfered. The inhabitation of p38/MAPK activity decreased the production of myocardial TNF-α, improved postburn myocardial contractile function, as well as enhanced tolerance of vitro cultured myocardial cells to hypoxia and burn serum (Ballard-Croft, White, Maass, Hybki, & Horton, 2001; Zhang, Ying, Chen, Yang, & Huang, 2008a). Zhang et al also found that p38/MAPK involved in burn-induced degradation of myocardial cell membrane phospholipids, and revealed that it achieved such effects by adjusting cytosolic phospholipase A2 (cPLA2) (Zhang et al., 2007b). Moreover, hypoxia was recently found to cause myocardial cell microtubule depolymerization through activation of p38/MAPK and change of phosphorylation level of microtubule associated protein 4 (MAP4) and oncoprotein 18/stathmin (Op18) (Hu et al., 2009). Additionally, through F-actin cytoskeleton rearrangement and phosphorylation of L-caldesmon, p38/MAPK conducted an important role in endothelial barrier dysfunction induced by burn serum (Chu et al., 2010).

The Rho-kinase pathway has been proved by other researches to perform a critical role in the reconstruction of cardiac muscle fibers after burn injuries (Hoshijima, Sah, Wang, Chien, & Brown, 1998; Kobayashi et al., 2002). The activation and up-regulation of α-1-adrenergic pathway (Ballard-Croft, Maass, Sikes, White, & Horton, 2002) led to activation of RhoA/Rho-kinase (Suematsu et al., 2001). Evidence showed that the myocardial Rho-kinase expression was considerably enhanced at 1 hour, 2 hours, and 8 hours post-burn, and engaged in regulating the synthesis and release of inflammatory factors like TNF-α、IL-1β and IL-6 by myocardial cells in rats with over 40% TBSA burns (Horton, Maass, & Ballard-Croft, 2005).

Protein kinase C (PKC) was also found by some researchers to engage in regulating myocardial inflammatory reaction and cardiac dysfunction. PKCε, a major PKC isoform in adult cardiomyocytes, presented up-regulated expression and increased activity after burn injury. The expression of PKCα was also up-regulated at early post-burn stage, while the PKCδ expression increased later (at 24 hours post-burn). Even though the impacts of each PKC isoform after burn injuries remain unclear, it has been confirmed that PKC pathway involved in the regulation of myocardial cytokine synthesis. The inhibitor of PKC, either calphostin or chelerythine, could significatly reduce inflammatory cytokines secretion by myocardial cells and improve the damaged myocardial contractile function (Horton, White, & Maass, 1998).

The transcription factor NF-κB, downstream of the PKC/p38/MAPK/JNK/Rho-kinase pathway, regulates a variety of genes of inflammatory cytokine, such as TNF-α and IL-1β, which are detrimental to cardiac function (Baeuerle & Baltimore, 1996). The level of myocardial NF-κB, according to Carlson et al's finding, continuously increased from 1 hour to 24 hours post-burn. The NF-κB activation started earlier than secretion of TNF-α and IL-1β by myocardial cells, which was again earlier than the occurrence of heart function impairment (Carlson et al., 2003). In further experiments, the NF-κB activity was inhibited by molecular or pharmacological approaches to explore its effect on myocardial inflammatory reaction and cardiac dysfunction. The NF-κB activity was elevated from 2 hours to 24 hours post-burn in wild-type mice. NF-κB nuclear translocation was not

detected in burned mice with over-expression of IκB. In contrast with wild-type burned mice, burn mice overexpressing IκB presented decreased secretion of TNF-α and IL-1β and less heart function impairment. ALLN, the specific NF-κB antagonist agent, can also prevent NF-κB nuclear translocation, inhibit the secretion of TNF-α and IL-1β, and improve cardiac functions (Carlson et al., 2003). These facts imply that activation of NF-κB was upstream of signal transduction pathway, which performs a critical part in the pathological progression of burn-induced myocardial damage and cardiac dysfunction.

Reports from our laboratory showed that both energy dysmetabolism (Liang, Tang, Yang, & Huang, 2002) and apoptosis (Zhang et al., 2008c) of myocardial cells induced by mitochondrial Ca^{2+} disorder after burns directly led to myocardial damage. Activation of tumor necrosis factor receptor-associated protein (TRAP1) and adenosine A1 receptor, however, inhibited the mitochondrial permeability transition pores (MPTP) to open, so as to prevent apoptosis provoked by MPTP opening and to achieve myocardial protection (Xiang, Huang, Shi, & Zhang, 2010a; Xiang et al., 2010b). We examined the RAS active ingredients and endothelin in serum and myocardial tissues at 10 minutes, 30 minutes, 1 hour, 3 hours, and 6 hours post-burn and found that concentrations of myocardial Ang II and its convertase ACE rose significantly since 10 minutes, while serum Ang II concentration increased notably since 30 minutes postburn, a little later. It demonstrated that the rapid activation of local cardiac RAS occurred earlier than the activation of circulatory RAS. Myocardial endothelin levels also increased 10 minutes after burns, and then maintained at a relatively higher level all the time. Serum endothelin levels, however, did not change much. Simultaneous myocardial blood flow measured by fluorescent microspheres also dropped at the same time point, suggesting these two strong vaso-excitor materials both involved in coronary vasoconstriction, resulting in cardiac insufficiency. Either ACEI or endothelin receptor blocking pharmacon could greatly improve myocardial perfusion, indicating the two substances' crucial roles in myocardial impairment. The rapid activation of local cardiac RAS after burns increased the Ang II level in myocardial tissues within a short period. Vasoconstriction it induced then resulted in myocardial ischemia and damage, which might be the most immediate cause of myocardial impairment at the early post-burn stage (Yang, Yang, & Chen, 1999).

Although the mechanism of myocardial damage and cardiac function depression in the early post-burn period has been explored and analyzed from various perspectives in multiple researches, it cannot be accurately explained only from a single aspect. The exact mechanism of myocardial damage may be the combined effects of multiple factors, or perhaps there are more convincing causes, which await our further investigation.

5. Prevention and therapy strategies of the burn-related myocardial damage/cardiac dysfunction

Based on the above-mentioned confirmed mechanisms of myocardial injury/decreased heart function, many scholars put forward the corresponding prevention and therapy strategies.

For the damage of inflammatory mediators to the myocardial function after burn injury, many studies have focused on limiting the adhesion and activation of the neutrophils. The monoclonal antibody specific for the intracellular adhesion molecule 1 and 2 (ICAM-1 and ICAM-2), P, L, E-selectin has been proved to be with hemodynamic and myocardial

protection effect during the treatment of the burns (Flynn, Buda, Jeffords, & Lefer, 1996; Horton et al., 1996; Mileski, Winn, Harlan, & Rice, 1991). Some scholars even selected the ICAM-1 and P-selectin knockout mice to explore the role of the adhesion molecules and neutrophil activation in treatment of the organ damage, particularly the myocardial damage/decreased cardiac function after burn injury

The most widely recognized clinical prevention and therapy means is to curb the oxygen free radicals damaging the organs, including clinical use of a large dose of the anti-oxidants. After burn injury, vitamin C and N-acetylcysteine can effectively improve the tissue energy load, improve the level of vitamin C and E in the tissues, enhance the elastase activity, enhance the microvascular function and inhibit production of the free radicals. The enhanced antioxidant capacity is helpful for maintenance of the high-energy phosphate level in the tissues, improvement local micro-circulation and effective prevention of the burn edema (LaLonde, Nayak, Hennigan, & Demling, 1997; Lalonde, Picard, Campbell, & Demling, 1994; Matsuda et al., 1992; Matsuda et al., 1991). Antioxidant therapy can protect the mitochondrial membrane integrity and thereby prevent cardiac dysfunction after burns (Zang, Maass, White, & Horton, 2007). Matsuda et al even found that the antioxidant vitamin therapy could reduce the planned amount of resuscitation fluid with an adequate cardiac output (Matsuda et al., 1993). Other experiments showed that the left ventricular systolic dysfunction, the continual increase of the preload and the coronary blood flow decrease in the rats with lack of vitamin antioxidant therapy, which, however, could be improve with the antioxidant treatment (Horton, 2003).

Ulinastatin (UTI), the refined protease inhibitors extracted from the human urine, can not only inhibit the activities of many hydrolytic enzymes including trypsin, phospholipase A2, hyaluronidase and elastase, but also prevent the MDF production and ameliorate the circulatory state of shock. The experimental and clinical studies have proved that UTI exerted a significant effect on prevention and treatment of the myocardial damage, for it could regulate the inflammatory response balance, remove the oxygen free radicals, reduce the lipid peroxidation and inhibit the myocardial apoptosis (Huang, Xie, Zhang, Dang, & Qiong, 2008).

For the patients with total burn area over 35% TBSA (of which 3rd degree burn over 20% TBSA), surgical removal of the entire eschar early after burn can reduce SIRS and endothelial system damage and hence effectively prevent the MODS (Huang, Yang, Chen, Crowther, & Li, 1999a). The mitochondrial damage is a key factor to myocardial apoptosis, which can be alleviated by using the mitochondrial stabilizers ruthenium red after burns (Wan-Yi, Hui, Zong-Cheng, & Yue-Sheng, 2002). The other measures such as antisense c-jun and p38 gene transfection (Huang & Hu, 2004; Huang et al., 2007) and hypertonic saline dextran (Horton, Maass, White, & Sanders, 2001b) also have certain curative effect.

6. Conclusion

In brief, the cardiac local RAS which is activated immediately after severe burns causing vasoconstriction results in ischemic and hypoxic injury in myocardiums, which contributes mostly and initially to the post-burn myocardial damage and heart dysfunction. The uncontrolled cascade response of the inflammatory factors, cytoskeleton and mitochondria destruction in cardiomyocytes, apoptosis and necrosis following ischemia and hypoxia are

directly responsible for the post-burn myocardial damage and cardiac dysfunction. And the cardaic pumping deficit with reduced output offers insufficient blood flow to the organs such as liver, kidney, and intestines, which induces and further aggravates the burn shock. In the pathophysiological course of severe burns, the myocardial damage/cardiac dysfunction and the burn shock (microcirculation disturbance and inadequate tissue and organ perfusion) are the two crossed main lines, the vicious circulation of which may lead the patients to MODS and even death. Can the originating factor for the myocardial damage be effectively blocked, the survival rate of the patients with extensive burns will be greatly improved. Thus, it is worthy of looking forward to a breakthrough in more in depth and effective endogenous protection mechanism of the myocardial damage.

7. Acknowledgment

8. References

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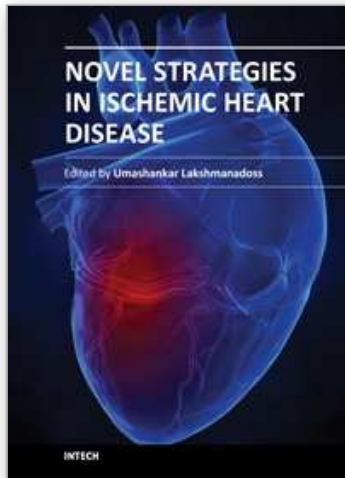
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