Micro-circulating hyperdynamic blood flow as a key pathogenic factor in early sepsis

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Abstract

Objective: Human research on sepsis has continually deepened over the years, entering the fields of molecular biology and genomics in the modern day. However, the pathogenesis of sepsis is yet unclear; and even its definition is still controversial. As specified in "International Consensus on Sepsis (3.0)" published in the *Journal of the American Medical Association* (2016), defining sepsis and septic shock can be a challenge; it is necessary to know the pathogenesis of sepsis more accurately, to accurately define it. As we have recently found in clinical practice, a sublingual micro-circulating and hyperdynamic blood flow is present in the early stages of sepsis. In our study, the necessity and universality of this phenomenon in different mammals was analyzed; a detoxifying mechanism and the Feng-Bernoulli warm shock mechanism were proposed for sepsis, and the pathogenesis of sepsis was inferred.

Methods: Through the intravenous injection of lipopolysaccharide (LPS), sepsis infection models were established for Bama miniature pigs and Japanese white rabbits respectively. Before and after the modeling, the variation and progress of blood flow rate in the same-branch sublingual capillaries were measured. Through cecum ligation and puncture (CLP) surgery, a sheep septic shock model was also established; and the correlation between micro-circulating hyperdynamic blood flow generation and macro-hemodynamic indices were analyzed. Through LPS injections of different doses into caudal veins, a mild injection and serious injection model was established for SD rats respectively, validating that the hyperdynamic blood flow in animal bodies as the manifestation for immune detoxifying mechanisms is necessary and universal.

Results: Before and after the modeling, blood flow rate in same-branch capillaries was separately 302 μm/s and 958 μm/s in Bama minipigs. Before modeling, mean blood flow rate in sublingual micro-circulating was 539 μm/s in Japanese white rabbits; in the early period after LPS injection, blood flow was accelerated to generate a hyperdynamic blood flow of mean >1000 μm/s. In the sheep CLP sepsis model, sublingual micro-circulating blood flow acceleration was present before the variation of cardiac index and cardiac output, Under the conditions of either mild infection or serious infection, hyperdynamic blood flow occurred in sublingual micro-circulating of rats; under the condition of mild infection, rats entered semi-sleep state after generation of hyperdynamic blood flow, which could be recovered by themselves; under the condition of serious infection, blood flow was stagnant after the generation of sublingual micro-circulating hyperdynamic blood flow, and rats died if there was no intervention.

Conclusion: In different mammals and different sepsis models, the phenomenon of micro-circulating blood flow acceleration occurs in the early period, which is necessarily universal. The phenomenon of sublingual micro-circulating blood flow acceleration comes before the variation of cardiac output, which should be key reasons for cardiac output variation. The blood flow acceleration can also accelerate the detoxifying effect, which is the process of immune defense reaction. However, the hyperdynamic blood flow and subsequent cardiac output increase will cause an oxygen exchange disorder, thus inducing warm shock. We have named the effect the Feng-Bernoulli warm shock mechanism, which is actually the primary pathogenesis for early sepsis or distributive shock.

Keywords: Sepsis; septic shock; micro-circulating; hyperdynamic blood flow; warm shock; Feng-Bernoulli warm shock

Study Background

Sepsis is a group of symptoms which are caused by infection, and can induce life-threatening organ dysfunction; it is a clinical syndrome with a high fatality rate. Sepsis not only seriously threatens human health, but also brings about huge economic burden on medical health. As shown by a Meta analysis of relevant studies on incidence rate and case fatality rate of adult sepsis in 27 developed countries in the period of 1979-2015, the annual incidence rate of sepsis was 288/100,000; in the past 10 years, the annual incidence rate of sepsis was about 437/100,000, with a case fatality rate of about 17%; the annual incidence rate of severe sepsis was about 270/100,000, with a case fatality rate of about 26% (Wang Zhong et al, 2020) [1]. Notably, Chinese relevant studies showed a higher case fatality rate of sepsis than that in developed countries (Wang Zhong et al, 2020) [1]. Although human research on sepsis has continuously expanded, and has entered the level of molecular biology and genomics, the pathogenesis for sepsis is yet unclear. Just as specified in the "International Consensus on Sepsis (3.0)" published in *Journal of the American Medical Association* (JAMA, February 2016), it is currently still a challenge to define sepsis and septic shock; first and foremost, sepsis is still a broad term applied to describe a process that has yet to be completely understood (Mervyn Singer et al, 2016) [2].

Under our sublingual micro-circulating imaging of sepsis patients, hyperdynamic blood flow was found, with a flow rate of >1000 μm/s, and generally 1500-3600 μm/s. These results are consistent with the results for sublingual micro-circulating imaging of 2 severe sepsis cases which were issued in the International Round-table Conference Report (2007); within the visual field in these two cases, the highest blood flow rate was 2622 μm/s and 1529 μm/s respectively (De Backer et al, 2007) [4]. See Attachment I.

By identifying the hyperdynamic blood flow in human microvessels, the initial threshold value of hyperdynamic blood flow is defined by us as 1.5 times the normal microvessel blood flow rate; the reasoning for this is given in Attachment II.

As proven by the study of (Verdant C et al, 2005) [32] and (Liu Wei et al, 2017) [33], under the condition of normal abdominal pressure, sublingual micro-circulating is highly related to visceral micro-circulating in animals. Therefore, in our study, the phenomenon of blood flow acceleration was mainly measured in sublingual micro-circulating of infection or sepsis in animals (such as pigs, sheep, rabbits and rats); possible reasons for said phenomenon and the detoxifying effect were also analyzed. As found by results of our study, the sublingual micro-circulating hyperdynamic blood flow in early sepsis found in clinical practice is a necessary and universal phenomenon when the sepsis occurs in mammals (including: human body); although it is a detoxifying process of body immune defense reaction, it causes Feng-Bernoulli warm shock. These findings are of great innovative significance for clarifying the pathogenesis and clinical diagnosis of sepsis.

Materials and Methods

Experimental animals

a: Guangxi Bama minipigs: 1 pig, provided by Laboratory for Animal Genetics and Breeding of Guangxi University, License No. SCXK(Gui)2018-0003, male, weight 27 kg.

b: Experimental sheep: 1 sheep, normal grade, male, age 18 months old, weight 26 kg, License No. SYXK(Lu)2021-0035, provided by HILE Biological Products (Shandong) Co., Ltd.

c: Japanese white rabbits: 22 rabbits, normal grade, provided by Pizhou Dongfang Breeding Co., Ltd., License No. SCXK(Su)2014-0005, male, weight 2.0-2.5 kg. These animals were randomly divided into a control group (6 rabbits) and LPS group (16 rabbits).

d. SPF rats: Provided by Changzhou Cavens Experimental Animals Co., Ltd., License No. SCXK(Xu)2016-0010, 3 male rats; weight: 434 g (No.1 rat), 410 g (No.2 rat), 455 g (No.3 rat). All animal experiments conformed to

relevant stipulations of Chinese governments on welfare and ethics of experimental animals.

Animal experiments of Class I:

A: Pig LPS model

In order to observe the phenomenon of micro-circulating blood flow acceleration and its correlation with sepsis progression, LPS (Sigma Co.) was injected intravenously. In Bama minipigs, 3% Pentobarbital was continuously injected intravenously at 8-10 mL/h to maintain anesthesia; and LPS 5 μg/kg was intravenously injected. Before and after LPS injection, the variation of blood flow rate in the same branch was observed and recorded in video; a comparison analysis was made for the variation of blood flow rate. After LPS injection, observation of sublingual micro-circulating was immediately begun.

B: Sheep CLP sepsis model

In order to explore the time progression for the phenomenon of high output and low resistance in macro-hemodynamics of sepsis and for the phenomenon of sublingual micro-circulating hyperdynamic blood flow in its micro-hemodynamics, cecum ligation and puncture (CLP) was performed on sheep. The experimental sheep were weighed. Into the muscle of hind legs, a Midazolam Injection 0.4 mg/kg and Sufentanil Citrate Injection 0.007 mg/kg was injected to sedate the subjects. After the animals fell asleep, they were kept in a supine position through protective constraints. After tracheotomy of the anterior cervical region, a #7.0 tracheal catheter was implanted. A ventilator was connected for mechanical ventilation (SC-3 invasive ventilator, Nanjing Puao Medical Equipment Co. Ltd., China). Through accessing the internal jugular vein, a double-lumen central vein catheter was implanted. Through this internal jugular vein, a Propofol Injection of 15 mg/kg/h and a Rocuronium Bromide for Injection 0.2 mg/kg were given for maintenance anesthesia. Parameters for the ventilator were adjusted as follows: ventilation mode of volume control; tidal volume 300 mL; positive end-expiratory pressure (PEEP) 5 cmH2O; fraction of oxygen inspiration (FiO2) 1; inspiratory to expiratory ratio (I/E) 1:2. An ECG monitor (Dash 2000, GE, GuoXieZhuZhun 20058730009, China) was connected for measurement of heart rate and non-invasive blood pressure. A sensor (FloTrac MHD8 cardiac output and Pressure Monitoring Sensor, Edwards Lifesciences LLC, Canada) was connected with the internal jugular vein for measurement of the central venous pressure (CVP). A Hemodynamic monitor (Vigileo MHM1E, Edwards Lifesciences, GuoXieZhuZhun 20063211962, USA) was connected with common carotid for measurement of cardiac output and cardiac index. Then, a septic shock model was established through CLP surgery. When mean arterial pressure dropped to 70% of normal blood pressure, the establishment of the septic shock model was considered successful. After successful modeling, observation of the sublingual micro-circulating was begun. At observation, all secretes were first cleared off of sublingual mucosa. Then, the LH-SDF-2 sidestream dark-field (SDF) vital microscope with disposable transparent protective sheath in the front of the probe was gently adhered to the sublingual lateral side (Note: Avoid an obvious compression on mucosa, so as not to influence the vascular engorgement. Adjust the focal length for obtaining of clear images).

Through the above vital microscope, software and Multi-angle adjustable bracket observations of whether the images of Blood flow in the same blood vessel acceleration appeared in sublingual micro-circulating of sheep before and after the modeling were made.

C: Rabbit LPS model

Japanese white rabbits were raised for one week in a desensitized environment. Before the surgery, they were made to fast for 24 hours. Into the vein at the margin of the ear, 20% Urethane 4-6 mL/kg was injected for anesthesia. After the tracheotomy, a tracheal catheter was implanted. A 24G polyethylene catheter was implanted into the common carotid. Through an pressure energy converter, a biological signal collection system (BL-420S, Chengdu Taimeng Instrument Co., Ltd.) for thalline alliance in Chengdu) was connected for continuous monitoring of invasive arterial blood pressure.

In LPS group, LPS 2 mg/kg (Sigma Co.) was injected into the vein at the margin of the ear; in the control group, LPS was not injected, but rather only normal saline of equal amount was injected. When mean arterial pressure dropped to 70% of blood pressure before LPS injection, the occurrence of sepsis was considered to have happened.

By localizing through the LH-SDF-2 SDF vital microscope,Then it was located on a microvessel larger than 20μm . After LPS injection, the observation was started. At the time point of 0min, 5min, 10min, 15min, 20min, 25min and 30min, videos were collected; the animals were kept immobile until the completion of video recording.

Animal experiments of Class II: detoxifying mechanism test

Rat LPS model

In order to assess the influence of hyperdynamic blood flow on the detoxifying ability of animals, LPS of different doses was injected into rats. After weighing the 3 rats, LPS 0.5 mg/kg (L8880, Solarbio) was injected into their caudal vein; with the dose being based on weight: 434 μL for No. 1 rat, 410 μL for No.2 rat, and 555 μL for No.3 rat (i.e. by an increase of 100 μL over the weight-based dose).

Measurement of sublingual micro-circulating

Through a LH-SDF-2 hand-held vital microscope independently developed by Xuzhou Lihua Electronic Technology Development Co., Ltd., sublingual micro-circulating images were collected; the video recording lasted about 20 seconds each time. At video recording, the instrument was placed and fixed into Multi-angle adjustable bracket in cohesion with the vital microscope; then, the probe of instrument was gently placed into the sublingual mucosa; gas bubbles under the lens were eliminated through normal saline gauze. The pressure was adjusted until larger microvessel blood flow and more obvious images of blood cell continuous flow were clearly found, so as to eliminate artifacts. Finally, the same microvessel was localized, which was then kept immobile until the completion of testing.

Analysis of micro-circulating blood flow rate

In micro-circulating images, clear erythrocytes or leukocytes in sublingual micro-circulating branches were traced. Through the independently-developed Chinese Advanced Microvessel Analysis & Comparison System software (Version 1.0, Xuzhou Lihua Electronic Technology Development Co., Ltd.), the passing distance of these blood cells within a certain time was analyzed to obtain the micro-circulating mean blood flow rate. In our study, hyperdynamic blood flow rate was not measured using the currently universal space-time method, the reason for this is given in “Discussion”. [10]

Statistical analysis

Through SPSS 22.0 software, the study data was analyzed. Measurement data was expressed with the mean value ± standard deviation (x ± s), which was tested through the variance analysis. $P<0.05$ indicates that the difference was statistically significant.

Results

(1) Animal experiments of Class I：The phenomenon of micro-circulating blood flow acceleration was reproduced; it was proven as necessary. It was determined that such phenomenon occurred in the early period of infection.

After LPS injection into pig sublingual micro-circulating , the vessel of same branches sublingual micro-circulating blood flow was gradually accelerated over 3-9 minutes.sublingual micro-circulating blood flow was gradually accelerated over 3-9 minutes. Concrete measurement and comparison before and after LPS

injections are shown in Figure 1.

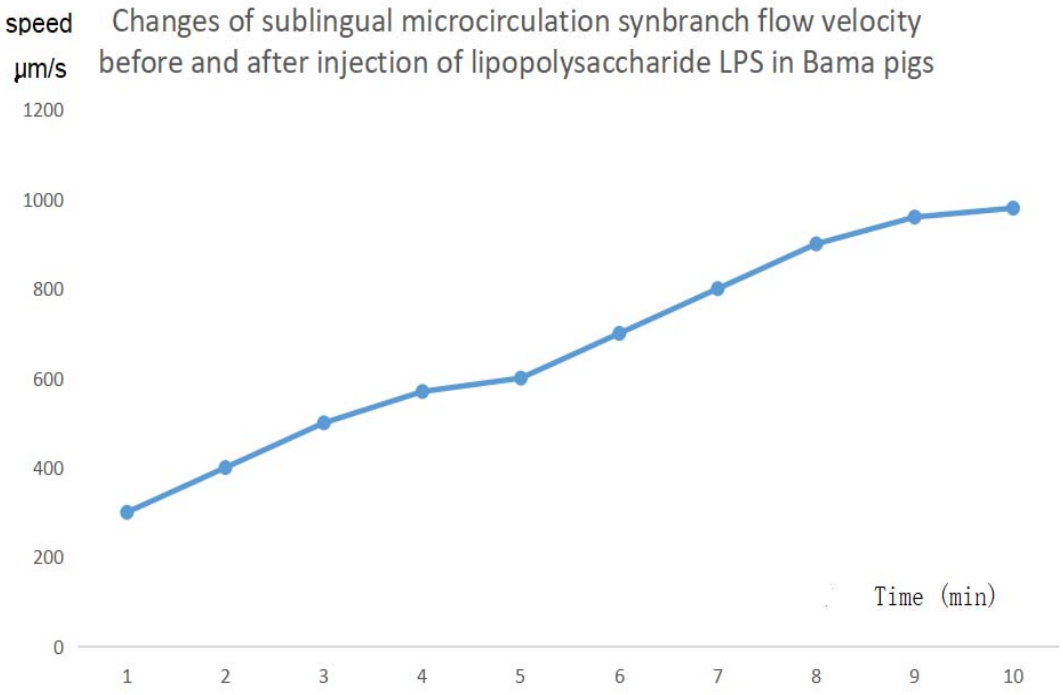

Figure 1: After LPS 5 μg/kg (Sigma Co.) was intravenously injected into Bama pigs, Blood flow velocity of the same branch of blood vessel gradually rose from 302 μm/s before the injection (Time 1) to 560 μm/s (Time 5, 5min), peaking at 958 μm/s (Time 9, 9min). Y-axis: Flow rate; X-axis: Time.

(2) The micro-circulating hyperdynamic blood flow in micro-hemodynamics was related to the macro-hemodynamic indices of cardiac output and cardiac index; and the phenomenon of blood flow acceleration was reproduced again; proving the necessity for its occurrence.

After CLP infection of sheep, the time variation was monitored for sublingual micro-circulating Blood flow velocity of the same branch of blood vessels,heart rate, cardiac output, cardiac index, mean arterial pressure and central venous pressure under continuous branch sublingual micro-circulating blood flow. Concrete detail was shown in Figure 2.

Surgery began at 10:00 on day 1. At 11:40, the model was established successfully. At 4:00 of the next day, measurement began. At the completion of surgery one day 1, the speed of sublingual micro-circulating blood flow, heart rate, cardiac output, cardiac index and mean arterial pressure (MAP) was measured; MAP was not significantly different from that of 4:00 the next day. Therefore, from 4:00 of the next day, the corresponding variation at the same time point was compared for the speed of sublingual micro-circulating blood flow , heart rate, cardiac output and cardiac index.

As shown by Figure 2, sublingual micro-circulating blood flow reached 190 μm/s at 4:00 of the next day (Time 1), 250 μm/s at 6:00 (Time 3), maximum 400 μm/s at 8:00 (Time 5), 350 μm/s at 10:00 (Time 6), and 150μm/s at 11:40 (Time 8.5) when the criteria for successful modeling was met. From Time 1 to Time 5, cardiac output was not increased synchronously with micro-circulating blood flow; it started to rise from Time 7 to Time 8. The variation trend of the cardiac index was similar to that of the cardiac output. The variation of the cardiac output and

the cardiac index lagged behind that of the micro-circulating blood flow; but the variation trend of the flow rate was same to the increase trend of the cardiac output and cardiac index.

Figure 2: Time variation of the speed of sublingual micro-circulating blood flow, heart rate, cardiac output, cardiac index, mean arterial pressure and central venous pressure during the establishing course of experimental sheep sepsis model.

(3) Prove the inevitability of accelerated blood flow in early sepsis from a statistical perspective

22 Japanese white rabbits were divided into the endotoxin group (16 rabbits) and control group (6 rabbits). In the endotoxin group, the variation of sublingual micro-circulating blood flow rate was observed after LPS injection; in the control group (without LPS injection), the variation of sublingual micro-circulating blood flow rate was

observed; results are shown in Figure 3. In the endotoxin group, the phenomenon of blood flow acceleration lasts >20 minutes; at 25min, blood flow rate was not obviously different between the two groups; after the occurrence of shock, the blood flow rate in the endotoxin group showed an obvious decreased than that of the control group. P<0.05 indicates that the difference was statistically significant. All values were expressed with mean value ± standard deviation.

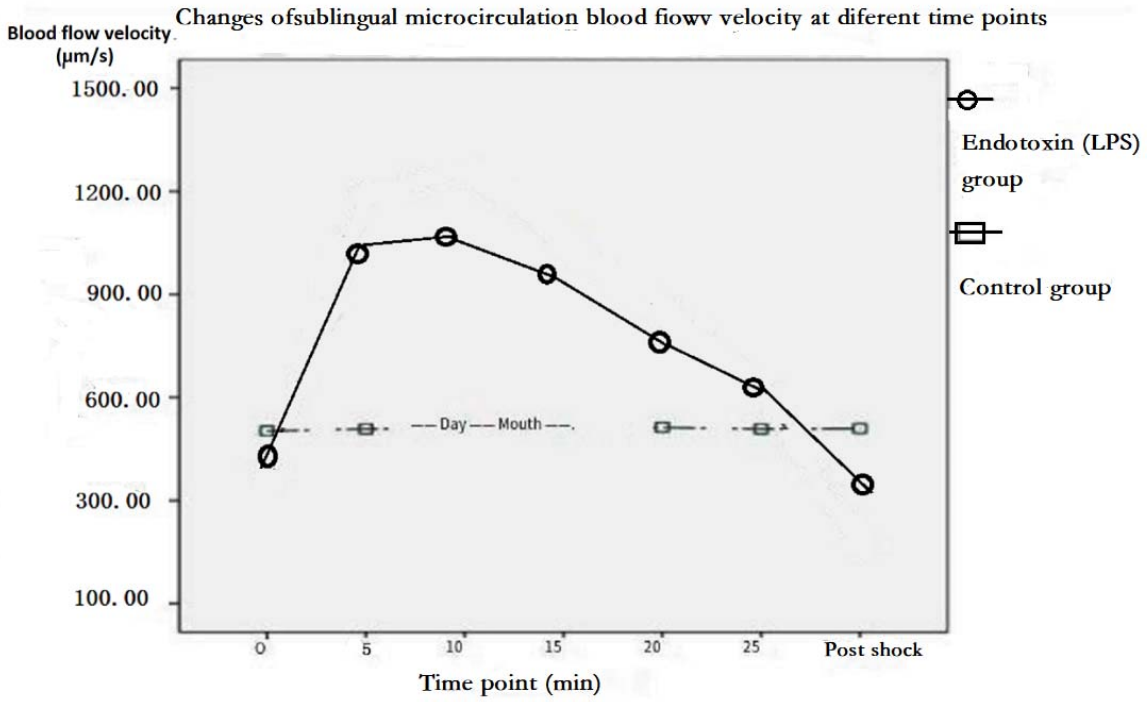

Figure 3: Comparison of the variation of sublingual micro-circulating blood flow rate between two groups. As more visually shown by such comparison, at 5-10 minutes after the injection, blood flow rate in the endotoxin group was increased by >1 fold compared to the control group; in the control group, the flow rate was steady and did not increase at all.

Animal experiments of Class II: to validate that animal body possessed a certain detoxifying mechanism

Rat No. 1; LPS injection into caudal vein: The branch sublingual micro-circulating blood flow rate reached 566 μm/s before the injection, 708 μm/s at 6 minutes after the injection and 1113 μm/s at 9 minutes after the injection.

Rat No. 2; LPS injection into caudal vein: The branch sublingual micro-circulating blood flow rate reached 130 μm/s before the injection and 340 μm/s at 8 minutes after the injection.

Rat No. 3; LPS injection into caudal vein: The dose was increased by 100 μL over the weight-based dose (i.e. 455 μL + 100 μL), The branch sublingual micro-circulating blood flow rate reached 200 μm/s before injection and 460 μm/s at 11 minutes after injection.

In rats No. 1 and No. 2, after LPS injection at experimental dose under anesthetic state, sublingual micro-circulating blood flow was accelerated; after resuscitation from anesthesia, toxic symptoms occurred; the rats did not eat or drink; and the response was lagging; within 24 hours of injection, the rats were in a semi-conscious state; after 24 hours, water drinking gradually begun; after 48 hours, vigor gradually restored; after 72 hours, response to human touch was restored, and the rats were indistinguishable from normal rats. In rat No. 3, the stagnant blood flow was gradually accelerated after 8 hours; and the rat died the next day.

Therefore, when the dose of LPS exceeds the detoxifying ability of animals, the animals will die. See Table 1.

Hyperdynamic blood flow may be a manifestation of initiation of the sympathetic-immune defense function.

When the invasion of toxins into the blood exceeds the detoxifying function of blood, the body initiates hyperdynamic blood flow so as to rapidly transport the toxins to the liver and kidney for detoxification. Therefore, this is actually an immune defense reaction which is formed by the body over the course of evolution. This is the detoxifying mechanism for generation of hyperdynamic blood flow.

Table 1: LPS injection into caudal vein at limited dose and at overdose

	Ctrotrol group		Observation group
Rat tail vein injection group	No.l limited injection	No.2 limited injection	No.3 Overdose injection
Weight	434 g	410 g	455 g
Injection quantity	434 uL	410 ul	455uL+100uL
Blood flow velocity before injection LPS into the same branching vessel （um/s）	566	130	200
Blood flow velocity after injection LPS into the same branching vessel for 8-12 minutes（um/s）	1113	340	460
Post-injection state	24-hour resumption of diet	24-hour resumption of diet	He died 24 hours later

Table 1: Experimental results after LPS injection at limited dose and at overdose into caudal vein of rat No. 1 and rat No. 2 under an anesthetic state. .

Discussion

In order to clarify the pathogenesis of sepsis, we first raised 5 questions, then answered them by combining the above experiments; then, according to experimental results, literature data and logic judgment, detailed proof was given for these answers; finally, such information was integrated into an innovative new scientific theory for the pathogenesis of sepsis.

1. Question 1: Is the hyperdynamic blood flow in sepsis a necessary and universal phenomenon? Answer 1 and Proof 1 are provided below.

Question 1 was raised according to the found sublingual micro-circulating hyperdynamic blood flow in human sepsis: At the beginning of our study, a hyperdynamic blood flow in human sepsis was measured according sepsis videos from relevant literature (De Backer et al, 2007) [4]. The question being, is hyperdynamic blood flow in sepsis a necessary and universal phenomenon?".

Answer 1: This phenomenon is an immune defense reaction formed by the human body over the course of evolution; the generation of hyperdynamic blood flow is the body’s detoxifying mechanism, and thus it is a necessary and universal phenomenon.

Proof 1: We first proved the necessity, and then proved the universality. Of course, a universal phenomenon is also

a necessary one.

As this phenomenon is necessary and universal, it should be reproduced in animal experiments. Therefore, animal experiments of Class I and II were designed. As proven by experiments on animals of different species and different quantity, blood flow rate of the same branching vessel after the establishment of an animal sepsis model is increased by >1 folds than before modeling. Therefore, the variation trend of sublingual micro-circulating blood flow acceleration in the early sepsis of animals is consistent with that in sepsis patients found in clinical practice; proving the judgment as necessary in Answer 1, i.e. micro-circulating blood flow acceleration (with manifestations of hyperdynamic blood flow in human body) is a necessary phenomenon of mammals (including: human beings) in early sepsis.

Proof for universality of hyperdynamic blood flow in early sepsis: The train of thoughts for this proof is shown as follows: Human beings universally realize a phenomenon of high output and low resistance in the macro-hemodynamics of sepsis; through the animal experiment of Class I on sheep, literatures, physiological theory and shock theory, a correlation between the hyperdynamic blood flow and the phenomenon of high output and low resistance was verified to thus prove that the hyperdynamic blood flow is universal for occurrence of sepsis (in fact, this is also proof for its necessity).

(1) Proof of experiment: As shown by the sequence of time axis in Figure 2 at animal experiments of Class I on sheep, micro-circulating blood flow was first accelerated, and an increase in heart rate, cardiac output, and cardiac index occurs approximately two hours after the onset of high dynamic blood flow in the microcirculation. This phenomenon indicates that the invasion of pathogenic factors was first perceived by vascular endothelial cells in peripheral micro-circulating; then, in order to avoid the further injury of human body, micro-circulating hyperdynamic blood flow is started to accelerate the detoxifying process. The micro-circulating hyperdynamic blood flow necessarily causes a large increase of venous return volume; therefore, in order to keep a dynamic balance, cardiac output is necessarily increased correspondingly. In other words, the micro-circulating blood flow acceleration is the reason for high output and low resistance in macro-hemodynamics; the micro-circulating hyperdynamic blood flow initiates the phenomenon of high output and low resistance in macro-hemodynamics. Since the micro-circulating hyperdynamic blood flow first starts slowly (i.e. the convergence and returning of arterial blood to the heart gradually increases), Therefore, there is a relatively lagging process reflected in the cardiac output CO,. This reveals an inherent correlation between the warm shock phenomenon of high output and low resistance in early sepsis and the phenomenon of sublingual micro-circulating hyperdynamic blood flow; it is proven that they are just different manifestations of same pathologic factor in macro-hemodynamics and micro-hemodynamics. As concluded in the literature (Ravikant T, Walt AJ et al, 1976) [15], (Christoph Langenberg, et al, 2006) [18] and (Auio S. HERMRECK, et al, 1969) [26], hyperdynamic blood flow occurs after the establishment of sepsis model for experimental pigs, sheep and dogs; since this phenomenon was not observed together with micro-hemodynamics, their inherent correlation was not revealed. Once the correlation between the micro-circulating blood flow rate in micro-hemodynamics and the cardiac output or cardiac index in macro-hemodynamics is ascertained, the universality of micro-circulating hyperdynamic blood flow in sepsis can be further realized by utilizing the human knowledge on that the high output and low resistance in macro-hemodynamics of sepsis is a universal phenomenon.

(2) Proof of literature: The high output and low resistance in macro-hemodynamics of sepsis is a unique universal phenomenon which has been realized for sepsis by human being. In Page 386 of the book “Prevention and Treatment of Sepsis”, Yong-Ming Yao et al specifies as follows: As shown by results of clinical observation and hemodynamic monitoring on numerous cases, septic shock patients were at a state of hyperdynamic circulation throughout most of the illness (i.e. cardiac output was normal or higher than normal value; total peripheral resistance was decreased); some patients were also at a hypodynamic in the latter period (i.e. low output and high

resistance) (Yaoyong Ming et al, 2018) [3]. In Page 125 of the physiological textbooks (9th edition), the following contents are mentioned in the part “blood circulation-micro-circulating”: At infective or toxic shock, arteriovenous shunt and thoroughfare channel is opened in large number; although the patients are in a state of shock, as the skin is warmer (i.e. warm shock is considered at this time); since a large amount of microarterial blood enters through anastomotic branch into the microvein and does not make material interchange with histiocytes, tissue anoxia can be aggravated to exacerbate the illness state (Zhuda Nian et al, 2018) [11]. Therefore, at infective or toxic shock, warm shock is a universal phenomenon. One piece of research (Liuda Wei et al, 2013) [5] states as follows: As a special type of shock, the infective shock usually has a sign of high cardiac output and low peripheral vascular resistance in macro-hemodynamics. In much of the foreign literature, the phenomenon of high output and low resistance in sepsis has also been proven: (Can Ince et al, 2018) [10], (Diamanno Ribeiro Salgado et al, 2011) [16], (A. M. Dondorp et al, 2008) [17], (Christoph Langenberg et al, 2006) [18], (Carolina Ruiz1 et al, 2010) [20], (Professor Emeritus John E et al, 2006) [22].

Animal experiments of Class I on sheep show a correlation between macro-hemodynamics and micro-hemodynamics. Therefore, the conclusion is as follows: As much of the literature has proven that the high output and low resistance in macro-hemodynamics is a universal phenomenon, the phenomenon of hyperdynamic blood flow in micro-hemodynamics is also a universal phenomenon.

(3) Proof of physiological theory: From the angle of physiological theory, the universality of hyperdynamic blood flow can be proven more sufficiently. In the physiological textbooks (Zhuda Nian et al, 2018) [11], the following contents are specified: Within a unit time, venous returned volume is equal to cardiac output; the venous returned volume means the volume of blood flow from vein into right atrium in every minute; the venous returned volume and cardiac output must be equal. In the American physiological textbooks ([31] Arthur C. Guyton et al, 2016), same viewpoints are also expressed: Venous return is the quantity of blood flowing from the veins into the right atrium each minute; the venous return and the cardiac output must equal.

Another literature report [5] specifies as follows: blood circulation in the human body is a closed loop; cardiac ejection volume is equal to venous returned volume; and thus, the cardiac output at physiological state is completely determined by venous returned volume. Therefore, hyperdynamic blood flow in micro-hemodynamics is of dynamic balance with the cardiac output. When micro-circulating massive hyperdynamic blood flow suddenly rushes into the vein, cardiac output is necessarily increased; even through the proof is not from animal experiments on sheep. Since the phenomenon of blood flow acceleration was found in above animal experiments, it can be immediately inferred that cardiac output is necessarily increased to cause the phenomenon of high output and low resistance. To be restated, as found in the images, sublingual micro-circulating hyperdynamic blood flow mostly occurred in microveins, because the blood in them all flows from multiple branches to single branch; as found in animal experiments, the hyperdynamic blood flow also mostly occurred in microvein, so that a massive blood flow to the microveins appears. According to the physiological theory, cardiac output is necessarily increased when blood flow volume in microvein shows a large increase, because this is required for maintaining a dynamic balance in the blood system. Therefore, we reversely inferred the phenomenon of high output and low resistance, along with the physiological principle that the venous returned volume must be equal to cardiac output; it can be proven that micro-circulating massive hyperdynamic blood flow occurs before the phenomenon of high output and low resistance in macro-hemodynamics.

Although only an increase of cardiac output in sepsis was found by us in the past, it can be inferred according to the above physiologic theory that the micro-circulating hyperdynamic blood flow necessarily first occurs before and during the cardiac output increase.

As proven above according to physiological theory, hyperdynamic blood flow in micro-hemodynamics causes a high output and low resistance in macro-hemodynamics of sepsis. Therefore, when we realize that the

high output and low resistance is universal, the hyperdynamic blood flow is also necessarily universal.

(4) Proof for universality from shock theory: Then, through the angle of shock classification and the heterogeneous phenomenon of micro-circulating blood flow in infective shock, the universality of hyperdynamic blood flow was proven again.

Due to the phenomenon of warm shock in distributive shock and the heterogeneous phenomenon of micro-circulating blood flow repeatedly revealed in the literature (Liuda Wei et al, 2013) [5], (De Backer et al, 2007) [4], (Can Ince at all.2018) [10], (Can Ince et al, 2015) [13] and (Bakker J et al, 2021) [27], the universality of hyperdynamic blood flow in early sepsis can be further proven.

In 1975, Weil et al. proposed a new method for shock classification according to hemodynamic characteristics: hypovolemic shock, cardiogenic shock, distributive shock and obstructive shock. These types of shock vary in treatment, and cover nearly all of clinical shock from the angle of hemodynamics. As found by Weil et al, different types of shock had different hemodynamic characteristics (Liuda Wei et al, 2013) [5].

The distributive shock is further classified into infective shock and neurogenic shock (which is caused by anesthetics overdose or nervous injury such as ganglion block and spinal shock), which varies in abnormal blood flow distribution.

See Table 14-3-2 in Page 190 of literature (Liuda Wei et al, 2013) [5].

Table 14-3-2 Clinical parameters and measurable related parameters of shock

Classify	skin	Right heart filling pressure	cardiac output	Left heart pressure	Vascular resistance	Myocardial oxygen
Hypovolemia	Cold, weak					
Cardiogenic	Cold, weak					
Infection (early stage)	Warm,red					
Infetive (late stage)	Cold, weak					
Sex spinal Cord	Cool Cool, Damage the red under the plane					
Obstructive	Cold, weak					

As shown in Table 14-3-2, the characteristics of warm skin (early stage of warm shock) was indicated only by infective shock and even not by neurogenic shock (spinal shock) which is another type of distributive shock.

From the angle of hyperdynamic blood flow, the logic of Answer 1 is as follows: the abnormal blood flow distribution (warm skin in early period and wet cold skin in late period) shown by infective type of distributive

shock and the blood flow heterogeneity reflected in the literature (De Backer et al, 2007) [4], (Liuda Wei et al, 2013) [5], (Can Ince et al, 2018) [10], (Can Ince et al, 2015) [13] and (Bakker J et al, 2021) [27] are actually two fragment processes at different stages of hyperdynamic blood flow in sepsis (i.e. occurrence, development and gradual disappearance); they both reflect the same phenomenon.

From the angle of hyperdynamic blood flow, we can explain how to form an abnormal blood flow distribution or heterogeneous phenomenon in an infective distributive shock. When sepsis starts to occur, numerous toxins enter blood, and human body initiates hyperdynamic blood flow to start detoxifying. Since hyperdynamic blood flow is gradually developed at this process, some blood flow is still normal during in this period; during the occurrence of this phenomenon, this is the first type of abnormal blood flow distribution in early sepsis, i.e. warm shock of high output and low resistance of blood flow or heterogeneous phenomenon of blood flow. When the sepsis is developed into the early and middle period, all blood vessels in micro-circulating are full of hyperdynamic blood flow; strictly speaking, the abnormal blood flow distribution or heterogeneous phenomenon does not exist at this stage; because the flow rate is basically all from hyperdynamic blood flow but warm shock still exists. When the sepsis enters middle-late period, due to the long-time lack of oxygen and nutrients, some of hyperdynamic blood flow are attenuated and then gradually substituted by stagnant blood flow; some of hyperdynamic blood flow still maintain the accelerated detoxification; at this stage, typical characteristics of abnormal blood flow distribution in distributive shock or the heterogeneous phenomenon of micro-circulating blood flow occurs again; this is the second type of distributive shock or heterogeneous phenomenon in the middle and late period (i.e. cold shock of low output and high resistance). To summarize, Both of these situations are a local process throughout the entire development of hyperdynamic blood flow in sepsis.. Therefore, Answer 1 explains the characteristics of distributive shock in infective shock at sepsis or the reasons for generation of heterogeneous phenomenon.

There are two states of distributive shock in infective shock. At the first state (i.e. high output and low resistance during the early stage), the hyperdynamic blood flow is gradually expanded; in this period, normal blood flow is still maintained inside some of blood vessels without conversion into hyperdynamic blood flow; this is the first type of abnormal blood flow distribution or is called as warm shock and heterogeneous phenomenon. At the second state (in middle-late period; low output and high resistance), the hyperdynamic blood flow gradually disappears and is attenuated; in this period, some or most of hyperdynamic blood flow are converted into stagnant blood flow, but some of blood flow still keep at a state of hyperdynamic blood flow; this is the second type of abnormal blood flow distribution or called as cold shock and heterogeneous phenomenon. As a difference of these two types of abnormal blood flow distribution, the stagnant blood flow does not coexist at abnormal blood flow distribution during the early period.

After the understanding of this process and by combining the medical consensus on distributive shock and blood flow heterogeneity universally accepted by literatures, a further understanding will be made for the necessity and universality of hyperdynamic blood flow stated in answer 1. As the medical community has realized, distributive shock (including: early warm shock) is a universal phenomenon, and hyperdynamic blood flow is also a universal phenomenon. Therefore, the universality of hyperdynamic blood flow can be verified through the concept of distributive shock which has been generally accepted in medical circle.

The warm type of distributive shock is characterized by high output and low resistance; as already proven by the above physiological theory, the phenomenon of high output and low resistance is actually caused by micro-circulating hyperdynamic blood flow. Therefore, as distributive shock is a universal phenomenon of shock, the hyperdynamic blood flow is also a universal phenomenon.

In our study, the necessity and universality of hyperdynamic blood flow was first proven for the following reasons: if the hyperdynamic blood flow is proven as necessary and universal, it very probably becomes an independent influencing factor for sepsis, which is worth of deep research.

However, in historic guidelines of surviving sepsis campaign (SSC), sepsis is defined as cardiac output >3.5 L/min/m2 in 2001 guideline; but the cardiac output measurement was discontinues following formal guideline updates issued in 2002. The possible reasons are given as follows: As an invasive or semi-invasive measurement method, the cardiac output measurement is not suitable for clinical measurement of early sepsis; in addition, since such phenomenon occurred during the early period, has unobvious characteristics and is usually difficult to perceive clinically, it is often be neglected in early sepsis.

2. Question 2: Why is the blood flow acceleration (or hyperdynamic blood flow) generated? Answer 2 of the “detoxifying principle” and Proof 2 are given.

In animal experiments of Class II on rats, Question 2 is raised: Why is the blood flow acceleration (or hyperdynamic blood flow) generated?

Answer 2 of “detoxifying principle”: The blood flow acceleration (or hyperdynamic blood flow) is a detoxifying process of the human body (i.e. sympathetic-immune defense process). When the toxins in the blood exceed the allowable rang.e of the blood , hyperdynamic blood flow will be initiated to rapidly transport the toxins into relevant viscera (such as liver and kidney) for detoxifcation.

Proof 2: After the intravenous injection of LPS at reduced doses into rats, capillary blood flow started to be accelerated; meanwhile, toxic symptoms of a semi-conscious state occurred (i.e. no eating/drinking, immobile at touch and no running/jumping). After the observation for 24 hours, the activity was gradually restored to food seeking and water drinking. Three days later, normal activity was completely restored to running/jumping as usual. However, if the dose of LPS exceeded the detoxifying ability of human body, the rats would die. Since this experiment shows that a self-detoxifying function exists in the immune defense system of animal bodies, Answer 2 is established. For the detoxifying function of various organs (such as liver, kidney and lung), a clarification has been made in Chinese and foreign textbooks of “Physiology,” as well as relevant literature (Zhuda Nian et al, 2018) [11], (Professor Emeritus John E et al, 2006) [22] and (Melanie J. Scott, Timothy R et al, 2008) [25]; it has been generally accepted and well known in the medical field. Therefore, it will not be stated any more herein.

3. Question 3: How to prove that the occurrence of accelerated (hyperdynamic blood flow) blood flow is for the purpose of "accelerating" detoxification?Answer 3 and Proof 3 are given.

For the detoxifying principle, Question 3, Answer 3 and Proof 3 are given.

Answer 3 and Proof 3 suggests that increasing the flow rate is necessary to accelerate detoxification.Logically speaking, assuming that the maximum amount of detoxification per cubic millimeter of liver cells is in the 100th percentile, the liver's detoxification function does not need to be maximized under normal circumstances, for example, when there are very few toxins in normal blood (there are also toxins in normal blood, but they remain below normal values throughout detoxification by the liver). Once a large amount of toxins appear, high-speed blood flow rapidly transports a large amount of toxins to the liver, enabling the liver to activate its maximum detoxification ability in the 100th percentile. This high-speed blood flow plays a role in accelerating detoxification and maximizing the detoxification function of liver cells.

Therefore, it is logically proven that Answer 3 of “accelerated detoxification” is established. Such aspects are clarified in the literature (Hangyul M et al, 2008) [14]. However, this literature only shows that the blood flow acceleration can accelerate the bacterial elimination; the accelerated detoxification is not attributed to the original motivation for the human body needs for detoxifcation.

Answer 2 and 3 of “accelerated detoxification” are reasons for the generation of hyperdynamic blood flow given for the first time in the field of sepsis. Understanding the phenomenon will enable further research on the pathogenesis of sepsis. In the field of sepsis, the phenomenon of hyperdynamic blood flow has been reported in

much of the foreign literature; but these literatures do not explain or understand the reasons for such phenomenon, they merely dispute the existence of hyperdynamic blood flow; this has influenced research on hyperdynamic blood flow. (De Backer et al, 2007) [4], (Vanina S et al, 2015) [8], (Vanina S et al, 2012) [9], (A. M. Dondorp et al, 2008) [17], (VS Kanoore Edul et al, 2015) [19], (Arnaldo Dubin et al, 2020) [23], (Bakker J et al, 2021) [27]. For example: the "Second Consensus on Sublingual Micro-circulating Assessment of Critical Patients" (2018, European Society of Intensive Care Medicine) specifies as follows: Although its origin and clinical significance still remains to be determined, the existence of hyperdynamic blood flow can be explained as micro-circulating variation (Can Ince et al, 2018) [10]. Its origin is determined through the principle of "accelerated detoxification" in Answer 2 and 3, which is our first step for solving the dispute on hyperdynamic blood flow.

Question 4: What adverse impact on the human body will be produced if the micro-circulating blood flow rate inside the true capillaries exceeds the normal limit? Answer 4 of "the hyperdynamic blood flow causes Feng-Bernoulli warm shock" and Proof 4 are given.

At present, classical theory (i.e. shunting theory) only explains the warm shock of high output and low resistance as follows: At infective or toxic shock, arteriovenous shunt and thoroughfare channels are opened in large numbers; the patients are in a state of shock, but with warmer skin (i.e. warm shock); since massive microarterial blood enters through anastomotic branch into microvein and does not make material interchange with histiocytes, tissue anoxia is aggravated to exacerbate the illness state (Zhuda Nian et al, 2018) [11]. However, this theory only gives indirect cause for warm shock, and does not directly explain whether the existence of hyperdynamic blood flow inside the true capillaries is related to warm shock.

The following diagram visually expresses the description of physiological textbooks (Figure 4-29 on Page 124).

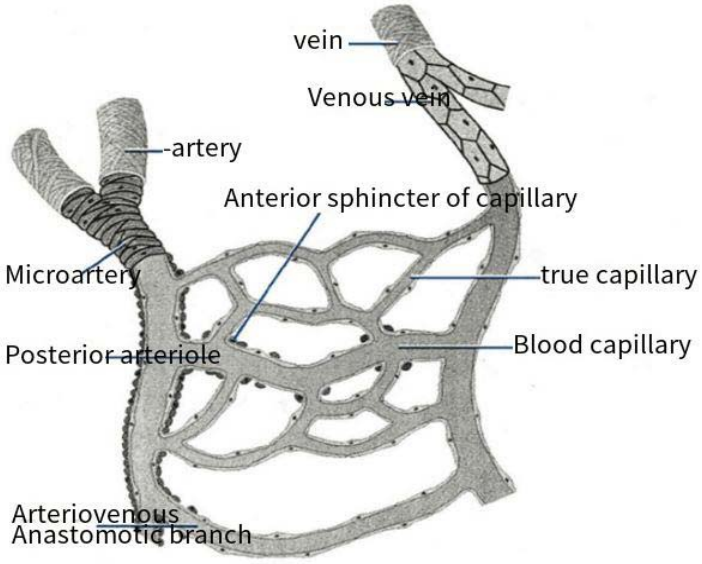

Figure 4-29 Composition Pattern Diagram of Microcirculation

We know that: Since the real site for oxygen exchange is the true capillary network, direct cause for oxygen exchange disorder is attributed to abnormalities inside the true capillary network. Then, there are four possible conditions for that massive microarterial blood enters through anastomotic branch into microvein and does not

make material interchange with histiocytes. Condition 1 (which is clarified in above textbooks): Since microarterial blood inside true capillary network enters through anastomotic branch directly into microvein (shunting theory), it is potentially inferred that this will cause a shunting and evacuation of blood inside the true capillary network; therefore, oxygen exchange disorder does not occur in blood inside the true capillary network; under this condition, there is no blood flow inside the true capillary network, meaning that internal respiration stops and the human body immediately dies by suffocation, and there will be no continuous phenomenon of the warm shock found in clinical practice; therefore, this condition does not conform to clinical facts. Condition 2: Inside the true capillary network, some blood still flows slowly, which does not consist with the results of our animal experiments, because the blood flow is accelerated; this also does not conform to the phenomenon of hyperdynamic blood flow in warm shock found in clinical practice; logically speaking, if some blood still flows slowly, clinical manifestations should be cold shock; however, the actual clinical manifestation is warm shock. Condition 3: Inside the true capillary network, all blood is stagnant and there is no perfusion or flow, which does not consist with the phenomenon of hyperdynamic blood flow found in the above animal experiments and the results of its clinical observation (De Backer et al, 2007) [4]. Therefore, only Condition 4 is applicable: Inside the true capillary network, the blood flows at a very high rate (called hyperdynamic blood flow), which is consistent with the results of experimental observation and the manifestations of clinical observation.

Therefore, oxygen exchange disorder may only occur in hyperdynamic blood flow inside the true capillary network and microveins; its reason can be attributed to the Bernoulli principle; it is called by us the Feng-Bernoulli warm shock mechanism, to distinguish it from the shunting theory in current textbooks. Next, we will make a deep theoretic exploration of the Feng-Bernoulli warm shock mechanism. This deep analysis will not only reveal the direct cause for warm shock, but also very probably reveal the pathogenesis for sepsis.

How the Bernoulli principle becomes the direct cause for warm shock is concretely proven in the following. In order to make such proof, we have to quote a large section of knowledge from the physiological textbooks [11], the understanding of the reader is appreciated.

(1) According to physiological theory, oxygen exchange and carbon dioxide exchange in the human body is determined by a difference in pressure. The physiological textbook (Zhuda Nian et al, 2018) [11] specifies the following: Tissue ventilation is the exchange in gas between blood in systemic circulation capillary and histiocytes. Between tissue ventilation and pulmonary ventilation, the similarity lies in mechanism and influencing factors; the difference is that the gas exchange occurs between the liquid medium (i.e. blood, tissue fluid and intracellular fluid) and the partial pressure difference of O2 partial pressure (PO2) and CO2 partial pressure (PCO2) between the two sides of the diffusion membrane. This varies with the intensity of intracellular oxidative metabolism and the volume of tissue blood flow. If the blood flow volume is unchanged and the metabolism is enhanced, a PO2 decrease and PCO2 increase will occur in the tissue fluid; if metabolic rate is unchanged and the blood flow volume is increased, a PO2 increase and PCO2 decrease will occur in tissue fluid. Due to the aerobic metabolism of cells, the utilization of O2 and the generation of CO2, PO2 will be as low as <30 mmHg, and PCO2 will be as high as >50 mmHg. When arterial blood flows through tissue capillary, O2 diffuses according to partial pressure difference from blood to tissue fluid and cells; CO2 diffuses from tissue fluid and cells to blood (Figure 5-11); due to the loss of O2 and the obtaining of CO2, arterial blood becomes venous blood.

Gas molecules move continuously in an astatic way. When gas pressure differences exist between different regions, gas molecules will make a net transfer from sites with high gas pressure to those with low gas pressure, this is known as gas diffusion. According to its own partial pressure difference, each of these mixed gases diffuse from sites of high partial pressure to those with low partial pressure until a dynamic balance is reached. Both pulmonary ventilation and tissue ventilation are accomplished using diffusion. The volume of gas diffusion within unit time is defined as the gas diffusion rate (D). Fick Dispersion law specifies as follows: When gas passes

through thin-layer tissue, gas diffusion rate is directly proportional to gas partial pressure difference between two sides of tissue (AP), temperature (T), diffusion area (A) and gas molecule solubility (S); but it is inversely proportional to diffusion distance (d) and square root of gas molecular weight (MW). The correlation of gas diffusion rate with each influencing factor is shown in the following formula below:

$$D \propto \frac{\Delta P \cdot T \cdot A \cdot S}{d \cdot \sqrt{MW}}$$

Gas partial pressure difference: Gas partial pressure means the pressure produced by each gas component of mixed gas. Under constant temperature, partial pressure of a certain gas is obtained by multiplying the total pressure of mixed gas and the volumetric ratio of this gas among mixed gas. For example: Air is a mixed gas with a total pressure of 760 mmHg, the O2 volumetric ratio is about 21% and PO2 is 760×21% = 159 mmHg; CO2 volumetric ratio is about 0.04%, and PCO2 is 760×0.04% = 0.3 mmHg. Gas partial pressure difference (□P) means the difference value in partial pressure of a certain gas between two regions; it is the dynamic force for gas diffusion and the key factor for determination of gas diffusion direction.

(2) Characteristics of Hb-O2 combination: This combining reaction is rapid (<0.01 seconds), reversible, and dissociates very rapidly. Both combination and dissociation do not require an enzymatic catalysis, but can be influenced by PO2. When blood flows through lungs with high PO2, Hb is combined with O2 to form oxyhemoglobin (HbO2); when blood flows through tissue with low PO2, HbO2 is rapidly dissociated to release O2 and become Hb. This process can be expressed through the following formula:

$$Hb + O_2 \underset{PO_2\,(Low,\ tissue)}{\overset{PO_2\,(high,\ lung)}{\rightleftharpoons}} HbO_2$$

(Zhuda Nian et al, 2018) [11]. Therefore, partial oxygen pressure difference is the direct dynamic force for the oxygen exchange.

(3) Bernoulli equation: $p + \frac{1}{2}\rho v^2 + \rho g h = C$, (Formula 3-6). According to the Bernoulli equation, the following phenomenon is shown. When an ideal fluid flows steadily inside the flow tube, the kinetic energy in unit volume, the gravitational potential energy in unit volume and the sum of pressure intensity at the site is constant. In the Bernoulli equation, three terms possess the dimension of pressure intensity: the term $\frac{1}{2}\rho v^2$ is related to the flow rate, and is often called dynamic pressure; the term p and pgh are unrelated to the flow rate; p is often called static pressure. If a fluid flows inside a horizontal tube (h1=h2), the potential energy of the fluid system is unchanged during the flowing course. Formula 3-6 can be written to Formula. 3-7: $p + \frac{1}{2}\rho v^2 = C$.

As shown by the above formula, fluids flowing inside horizontal tube have a pressure intensity that is larger at sites with a low flow rate; and a pressure intensity that is smaller at sites with a high flow rate [34].

(4) Gas partial pressure means the pressure produced by each gas component of mixed gas. When under constant temperature, partial pressure of a certain gas is obtained by multiplying the total pressure of mixed gas and the

volumetric ratio of this gas in a mixed gas [11].

(5) According to Bernoulli equation (Formula 3-6 and 3-7), the following phenomenon is shown. When blood flow rate is increased to a certain extent, the pressure intensity of arterial blood drops to reduce the oxygen partial pressure, making it difficult for oxygen molecules in arterial blood to enter tissue fluid for the oxygen supply of cells by relying on oxygen partial pressure difference, which causes oxygen exchange disorder (i.e. warm shock). This is just the basis for warm shock being caused by hyperdynamic blood flow inside true capillaries and microveins, called Feng-Bernoulli warm shock.

The direct cause for warm shock is explained above, through the Feng-Bernoulli warm shock mechanism. The current textbooks are just unilateral for the shunting theory of warm shock. This will lay a solid foundation for revealing the pathogenesis of sepsis.

In addition, the logic for Answer 4 is as follows. If the source of infective toxins exists continuously, a hyperdynamic blood flow will be continuously generated according to the principle of “accelerated detoxification” mentioned in Answer 2 and 3; at the continuous micro-circulating hyperdynamic blood flow, chronic anoxia will be caused in the human body, the clinical manifestations of which are warm shock symptoms of sepsis with high output and low resistance (Yaoyong Ming et al, 2018) [3], (Liuda Wei et al, 2013) [5], (Zhuda Nian et al, 2018) [11], (Diamantino Ribeiro Salgado et al, 2011) [16], (A. M. Dondorp et al, 2008) [17], (Carolina Ruiz1 et al, 2010) [20], (Professor Emeritus John E at all.2006) [22].

If intervention and rescue are not implemented, the continuous warm shock will cause anoxia and nutrient deficiency of cells/organs, which will start to fail. Then, the hyperdynamic blood flow is also gradually attenuated, and the stagnant blood flow is gradually increased correspondingly ,I. e. the beginning of "cold shock" ; this is micro-circulating blood flow heterogeneity as revealed in the literature (Paul WG Elbers et al, 2006) [6], (Vanina S et al, 2015) [8], (Vanina S et al, 2012) [9] and (Can Ince et al, 2018) [10]. Finally, this state transitions to cold shock, subsequent disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS).

If the mechanism of accelerated detoxification in Answer 2 and 3 explains the principle of immune defense function in human body and provides a train of causal thoughts for generation of hyperdynamic blood flow, the Feng-Bernoulli warm shock mechanism explains the direct pathogenesis of hyperdynamic blood flow for how to cause oxygen exchange disorder and thus induce warm shock in early sepsis,And then it also explained the cause of cold shock.

Answer 2 and 3 states: The generation of hyperdynamic blood flow is a spontaneous compensatory reaction of human body (i.e. detoxifying effect). This has a certain advantages for human body. However, since any matter is double-sided, the hyperdynamic blood flow also has side effects unfavorable for human body. We utilize the Feng-Bernoulli warm shock mechanism to explain the disadvantages of hyperdynamic blood flow that oxygen exchange disorder is caused to induce warm shock. This mechanism may be greatly significant not only from various angles (such as exploration of pathogenesis and finding of medical science) but also for guidance on clinical work and research work.

In fact, the oxygen exchange between blood and cells is influenced by many factors, such as erythrocyte deformability, capillary density, hematocrit and blood flow rate. However, we should find out main influencing factors oxygen exchange under particular conditions. When in a normal state, the above factors can influence the oxygen exchange; under the state of hyperdynamic blood flow, they can not become main influencing factors because the difference is too large between internal and external pressure of the capillaries, but the blood flow acceleration beyond normal limits will become main influencing factors. Of course, hyperdynamic blood flow can

be considered as a main influencing factor for oxygen exchange only under the premise that the effect of the Bernoulli principle should be understood and can be utilized to explain the reasons for oxygen exchange disorder (i.e. warm shock). If the Bernoulli principle is not understood, there is no way to grasp this main factor. For example: In the literature (A. M. Dondorp et al, 2008) [17], it is considered that the hyperdynamic blood flow can not cause an oxygen exchange disorder.

Question 5: Where does the direct dynamic force for hyperdynamic blood flow come from? Answer 5 of the "pulling principle" and Proof 5 are given.

Regarding the source of direct dynamic force for hyperdynamic blood flow, the physiological textbook (Zhuda Nian et al, 2018) [11] proposes the following: in infective or toxic shock, arteriovenous shunt and thoroughfare channels are opened in large number. This can illuminate our research.

Answer 5: In early sepsis, micro-circulating thoroughfare channels and arteriovenous anastomotic branch are opened in large number to pull the blood flow acceleration to the microveins (which is called the pulling principle).

Proof 5: In fact, this is also an embodiment of the Bernoulli principle. After the micro-circulating arteriovenous anastomotic branch is opened, a negative pressure is formed for the blood flow inside the true capillary exchange network and microveins to produce a sucking effect. See the following Figure 4:

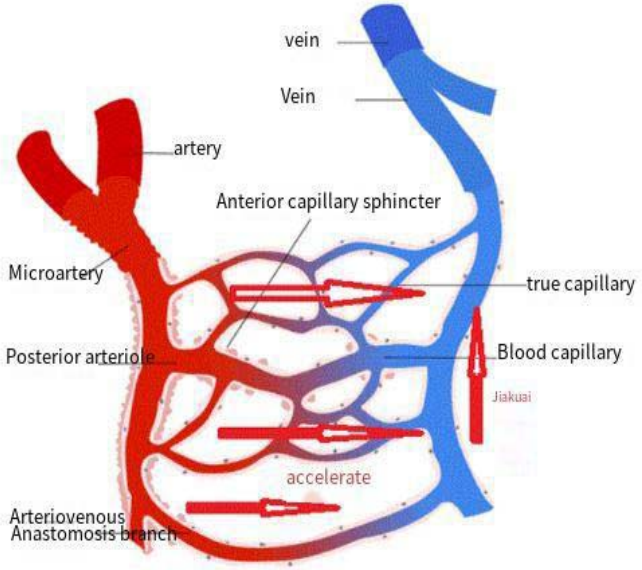

Figure 4:After a short circuit in the blood flow of the anastomotic branch, the accelerated flow pulls the blood flow of the true capillaries, generating hyperdynamic blood flow.

Therefore, the shunting theory in physiological textbooks states the following: Due to shunting of the anastomotic branch, some blood can not participate in oxygen exchange, meaning it cannot become a main or direct cause. Since blood flow exists in true capillaries, the main and direct cause for oxygen exchange disorder is abnormalities in the true capillaries (i.e. occurrence of hyperdynamic blood flow).

Conclusion: According to the above studies, we propose the following pathogenesis of sepsis.

Through overall consideration of the above five questions and the corresponding answers and proofs, we

clarify the pathogenesis of sepsis as integrally as possible from the angle of micro-circulating hyperdynamic blood flow. At the beginning, the toxins invade from wounds into the blood system; when numerous toxins are found in blood, the human body will begin hyperdynamic blood flow to rapidly transport the toxins to relevant organs (such as liver and kidney) for detoxifcation. As side effects of this process, blood flow inside the true capillaries is so rapid that it exceeds the normal limit of micro-circulating blood flow rate in human body (i.e. V>1000μm/s, Attachment II). According to the Bernoulli principle, in capillaries with blood flow acceleration, the pressure is necessarily decreased to reduce the oxygen partial pressure inside the blood vessels and decrease the difference between internal and external oxygen partial pressure in the capillary walls, so that most oxygen molecules have difficulty in making a normal diffusion outside the blood vessels for the oxygen supply of cells, which causes oxygen exchange disorder. Due to the effect of detoxifying principle, the toxins continuously invade from the wound into the blood system usually, within a few days. Due to the pulling principle, hyperdynamic blood flow continuously occurs in the human body under the action of the immune defense system, which causes Feng-Bernoulli warm shock. The occurrence and development of shock is a continuous process: presenting as warm skin and basically normal blood pressure in Feng-Bernoulli warm shock; and wet, cold skin, piebald formation and blood pressure decrease in cold shock. If timely treatment is not given at the stage of warm shock, cells and organs cannot obtain oxygen and nutrients as usual over a period of time; in continuous warm shock, hyperdynamic blood flow is gradually attenuated, and stagnant blood flow is gradually increased; the human body will gradually enter the stage of cold shock, with wet, cold skin and a blood pressure decrease, and typical symptoms of septic shock will occur (i.e. typical manifestations of infective type of distributive shock) If effective treatment is not yet given, DIC and MODS will ultimately occur. From the angle of micro-circulating hyperdynamic blood flow, the whole development process of pathogenesis of sepsis is explained. As the cause for warm shock, cold shock and MODS, the hyperdynamic blood flow in sepsis very probably becomes main pathogenesis of sepsis.

Our theory on the pathogenesis of sepsis also answers the following query of literature (Can Ince et al, 2018) [10]: Although its origin and clinical significance still remain to be determined, the existence of hyperdynamic blood flow can be explained as micro-circulating variation.

Sepsis is defined as a life-threatening organ dysfunction caused by host-response disorder under infective conditions (Mervyn Singer et al, 2016) [2]. The theory for sepsis pathogenesis through hyperdynamic blood flow meets three elements of this definition: infection, host response disorder and life-threatening organ dysfunction. Moreover, this theory clarifies the concrete organs and phenomenon of host response disorder: firstly, the host is just the blood flow inside micro-circulating true capillaries; secondly, in host response disorder (i.e. hyperdynamic blood flow occurs inside true capillary for a long time), internal environment steady state of blood flow is destroyed to cause oxygen exchange disorder (i.e. Bernoulli warm shock); finally, the continuation of anoxia in warm shock causes cold shock to induce MODS.

From the angle of hyperdynamic blood flow, we propose the theory of sepsis pathogenesis. There are two foremost innovative basic principles: one is the detoxifying principle; and the other is Feng-Bernoulli warm shock mechanism. These two innovative principles are the cornerstone for pathogenesis of sepsis.

In order to correctly find hyperdynamic blood flow, a reference should be made to Attachment III “Inclusion criteria for hyperdynamic blood flow sample of clinical sepsis, suggestions/precautions for sampling method and limitations of common space-time method in measurement of hyperdynamic blood flow”

Potential clinical significance of theory for sepsis pathogenesis

As is already known, the sepsis positive rate is very low in blood culture tests in clinical practice (Lin-hong Yuan, J.2018 et al) [28]. Blood culture as the golden standard requires a long time to find pathogens; up to 70% of

sepsis patients have received anti-infective treatment; so as to influence the finding time and positive rate of pathogen. Therefore, it possesses a very important clinical value to seek for more rapid specific indices for clinical diagnosis of sepsis (Lu-qiu Wei, et al) [35].

Firstly, we should realize that the human body can be compared to a highly-sensitive and accurate biological laboratory. It possesses a very high accuracy for finding of various pathogens for the following reasons: through the evolution of more than 0.1 billion years, the human body possesses a very strong ability for pathogen identification; otherwise, human beings will be die off at a young age by nature according to the law of survival of the fittest. Now, to determine if the test results of this medical laboratory and the immune defense process for initiation of hyperdynamic blood flow inside human body; particularly, the correct understanding of this process will bring about very good potential practical indices for clinical practice. We realize that: the human body is a highly-sensitive and accurate laboratory; by utilizing this laboratory, sepsis can be accurately and specifically diagnosed early.

Clinical value 1: Early and ultra early detection of sepsis , i.e. when the hyperdynamic blood flow of sepsis has just occurred.

Clinical value 2: As specified in “International Consensus on Sepsis (3.0)” (Mervyn Singer et al, 2016) [2], work groups have attempted to differentiate the sepsis from simple inflammation. Such differentiation is very simple, Because simple inflammation does not cause the appearance of hyperdynamic blood flow . For example: Among two inflammation patients, sublingual hyperdynamic blood flow occurs in one patient, but micro-circulating is normal in the other patient; the former develops into sepsis, but the latter is simple inflammation.

Clinical value 3: Hyperdynamic blood flow is utilized for accurate judgment of sepsis in the early, middle and late period, so as to make a scientific judgment of prognosis and take different measures for rescue/treatment. Manifestations in different periods of sepsis have been stated above: In the early period, hyperdynamic blood flow occurs to indicates that the human body will begin the detoxifying process; in the middle-late period, hyperdynamic blood flow starts to be attenuated and substituted by stagnant blood flow; in the late period, there is necessarily no blood perfusion/flow. In the literature (Vanina S et al, 2015) [7], hyperdynamic blood flow was not found, possibly because the sepsis was not staged. The literature (Zhangxiao Lei et al, 2021) [29] and (Geri et al, 2019) [30] state as follows: as compared with that with hyperdynamic blood flow, 30-day cumulative survival rate was lower in patients with stagnant and dilutive blood flow, and the difference was statistically significant; indicating that the hyperdynamic blood flow only occurs in early sepsis. In the middle-late period and late period, the stagnancy and no perfusion/flow of blood is a necessary physiological phenomenon. As compared with the stagnancy and no perfusion/flow of blood, hyperdynamic blood flow only occurs in early period. When hyperdynamic blood flow starts to be attenuated, some blood flow becomes stagnant; the other blood still maintains the state of hyperdynamic blood flow; this is middle period. Therefore, this is logically a necessary conclusion.

Clinical value 4: The international requirement is realized that the duration of bundle treatment should be shortened from 3 hours to 1 hour. When numerous toxins occur in blood, the human body starts hyperdynamic blood flow for detoxification. Once this process is found, various preparatory work can be made in advance and even at shorter time than 1 hour required for bundle treatment (In fact, we have already predicted sepsis 12 to 24 hours ahead of schedule, providing more ample preparation time for cluster therapy (clinical cases are expected to be published next year).

Secondly, as found in our study, there are two forms of hyperdynamic blood flow. The first form,Since this behavior is akin to a waterfall, therefore,the hyperdynamic blood flow in microvessels with a diameter of 50-100 μm is called “waterfall blood flow”.The second form,Since this behavior is akin to a swarm of flying mosquitos, the hyperdynamic blood flow in thinner blood vessels with diameter of <20 μm is called “ flying mosquitos blood

flow". Such denomination can facilitate a rapid identification of hyperdynamic blood flow in clinical practice.

In “International Consensus on Sepsis (3.0)” (Mervyn Singer et al, 2016) [2], the sepsis defined as the life-threatening organ dysfunction is caused by host-response disorder at infection; this new definition emphasizes that the host response disorder plays a crucial role in infection. Although such judgment is correct, concrete manifestations of host-response disorder are yet unknown. There is an urgent clinical need to know the manifestations of host-response disorder, so as to apply them for clinical guidance in life-saving care. As shown by our study, the host should be the blood flow inside true capillary network; during host-response disorder, micro-circulating hyperdynamic blood flow exceeds the upper limit of normal value in human body to cause Bernoulli warm shock; therefore, the micro-circulating hyperdynamic blood flow was exactly the concrete forms and characteristics of host response disorder. This solves the query mentioned in “International Consensus on Sepsis (3.0)”: “The task force recognized that no current clinical measures reflectthe concept of a dysregulated host response”.

Finally, an analysis was made for the relation between the current knowledge on sepsis pathogenesis in Chinese and foreign medical circle and the viewpoints in our study. It took a long time for humans to discover sepsis. The international definition of sepsis has changed from Version 1.0 in 1991 to Version 3.0 in 2016. The field for sepsis pathogenesis has also expanded to frontier scientific fields (such as cytobiology, genetics, immunology, molecular biology and genomics) (Yaoyong Ming et al, 2018) [3]. In early sepsis, pro-inflammatory and anti-inflammatory reactions occur; the main change of non-immune channels are complicated (such as cardiovascular system, nerve, autoregulation, endocrine, biological energy, metabolism and blood coagulation); there are multichannel molecular characteristics (such as transcription, metabonomics and proteomics) (Mervyn Singer et al, 2016) [2]. The pathogenesis and manifestations of sepsis have been discovered from various aspects: bacterial pathogenic factors; effects of inflammatory mediator; relations between endothelial cell injury (permeability of endothelial cells) and micro-circulating disorder; systemic inflammatory reactions; blood coagulation dysfunction; genetic polymorphism; high metabolism; mitochondrion oxygen utilization disorder; disseminated intravascular coagulation; apoptosis; immunosuppression and apoptosis; enteric bacteria and bacterial endotoxins (LPS) translocation; neuro-endocrino-immune network) (Yaoyong Ming et al, 2018) [3], (Fu Yuan et al, 2014) [12], (Linhong Yuan et al, 2018) [28]. However, the primary and main cause should attract attention. As shown by our study and clinical literatures (Yaoyong Ming et al, 2018) [3], ((Liuda Wei et al, 2013)) [5] and (Zhangxiao Lei et al, 2021) [29], the chronic anoxic state caused by hyperdynamic blood flow accompanied the body from early period of sepsis (3 minutes after LPS injection) until the death. During the developing course from hyperdynamic blood flow to stagnant blood flow and from warm shock to cold shock, the anoxic state is probably the primary and main cause among numerous mechanisms for sepsis pathogenesis. Due to long-time anoxia, normal immune defense function in human body declines to cause the occurrence of a series of disorders.

For example: If a mammal is suffocated by airway obstruction, it will necessarily die within a short time. During this course, every internal steady-state system of body will necessarily be destroyed. If the above pathogenesis is detected in time, a series of abnormalities will necessarily be found in terms of physiology, pathology and biochemistry (Mervyn Singer et al, 2016) [2], such as the variation at the level of cell and molecular structure. However, We should not forget that the primary and main cause is the anoxia caused by airway obstruction.

In scientific research, changing the angle of study is one way to further understanding of a problem. Through the research sepsis from the angle of hyperdynamic blood flow, the mysterious pathogenesis of sepsis may ultimately be revealed.

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Conflict of Interest

X. H. Feng is the Technical Director of Xuzhou Lihua Electronic Technology Development Co., Ltd. The other authors declare that there is no conflict of interest.

Author contributions

X.H. Feng conceived the study, directed the study ,and directed the bulk of the experiments.

Bu-Wei Yu reviewed and revised the article.

Y. Zeng carried out animal experiments , and provided theoretical evidence on the relationship between macroscopic hemodynamics and microcirculation Hyperdynamic blood flow.

Y.B. Sun Conducted animal experiments, data collection and calculations, and wrote articles on a part of the experiments.

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