

Microcirculation during cardiac arrest and resuscitation

Michael Fries, MD; Max Harry Weil, MD, PhD, FCCM; Yun-Te Chang, MD; Carlos Castillo, MSEE; Wanchun Tang, MD, FCCM

Objective: Direct observations of the microcirculation using orthogonal polarization spectral imaging have attracted attention and revealed that, especially in cardiogenic and distributive shock, there is discordance between the macrocirculation and the microcirculation. We evaluated serial changes and the effects of epinephrine on microcirculatory blood flow in the most severe form of circulatory failure, namely, cardiac arrest.

Design and Setting: Controlled laboratory animal study.

Subjects and Interventions: A total of 15 pigs were subjected to 5 mins of ventricular fibrillation and 5 mins of precordial compression before electrical defibrillation was attempted. In a subset, six animals received 1 mg of epinephrine after 1 min of precordial compression.

Measurements and Main Results: Microcirculatory blood flow was visualized in the sublingual mucosa at baseline and 0.5, 1, and 5 mins of ventricular fibrillation, at 1 and 5 mins of precordial compression, and at 1 and 5 mins after return of spontaneous circulation. In addition, coronary perfusion pressure was re-

corded. Microcirculatory blood flow decreased dramatically in the 0.5 min after the onset of ventricular fibrillation. Precordial compression partially restored microcirculatory blood flow in each animal but to a significantly greater extent in animals that achieved return of spontaneous circulation. These changes were paralleled by similar changes in coronary perfusion pressure. Both variables were highly correlated. Administration of epinephrine resulted in a massive reduction of microcirculatory blood flow that lasted for ≥ 5 mins.

Conclusions: In this model, microcirculatory blood flow was highly correlated with macrocirculatory hemodynamics, including coronary perfusion pressure in distinction with septic shock. Administration of epinephrine dramatically decreased microcirculatory blood flow. (Crit Care Med 2006; 34[Suppl.]:S454-S457)

KEY WORDS: microcirculation; macrocirculation; cardiopulmonary resuscitation; precordial compression; orthogonal polarization spectral imaging; ventricular fibrillation; coronary perfusion pressure

Modern cardiopulmonary resuscitation aims to promote forward flow of oxygenated blood to maintain heart and brain viability until return of spontaneous circulation (ROSC) (1). In experimental settings, the importance of restoring critical levels of coronary and cerebral blood flows for successful resuscitation during circulatory standstill has been securely documented (2). However, systematic clinical studies emphasizing especially the role of a minimal coronary perfusion pressure (CPP) to restore function of an arrested heart were not undertaken until the 1990s (3). Clinically, the measurement of CPP is limited exclu-

sively to patients who have catheters in place in the aorta and the right atrium. However, these microcirculatory variables do not necessarily reflect the state of that huge compartment of the vascular system, namely, the microcirculation (4). New technical advances using linearly polarized light to visualize red blood cells allow for real-time observation of the capillary exchange beds in various tissues (5, 6). The dynamic changes in microcirculatory blood flow in the setting of cardiac arrest and resuscitation are not as yet known. We herein report on prospective laboratory animal studies on serial changes in microcirculatory blood flow during cardiopulmonary resuscitation, together with the effects of epinephrine on microcirculatory flow.

MATERIALS AND METHODS

The studies were approved by the Animal Use and Care Committee of the Weil Institute of Critical Care Medicine. The institute's laboratories are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALACI). Experiments were performed on 15 male domestic pigs weighing between 35 and 40 kg (7, 8).

Study Groups. We first investigated serial changes in both macrocirculatory and microcirculatory blood flow from the onset of circulatory standstill, during precordial compression, and after ROSC, including outcomes in nine animals. In a second study, the effects of a single bolus of 1 mg of epinephrine administered after 1 min of chest compression were evaluated and compared with effects of saline placebo.

Animal Preparation. Animals were fasted overnight except for free access to water. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg) and completed by ear vein injection of sodium pentobarbital (30 mg/kg). Additional doses of sodium pentobarbital, in increments of 10 mg/kg, were administered for maintaining anesthesia. A cuffed endotracheal tube was advanced into the trachea, and the animals were mechanically ventilated with a volume-controlled ventilator (MA-1, Puritan-Bennett, Carlsbad, CA). End-tidal CO_2 was monitored with an infrared analyzer (01R-7101A, Nihon Kohden, Tokyo, Japan). Tidal volume was maintained at 15 mL/kg and FIO_2 at 0.21. Respiratory frequency was subsequently adjusted to maintain end-tidal CO_2 between 35 and 40 mm Hg.

For the measurement of aortic pressure, a fluid-filled catheter (DLR-7H, Braintree Scientific, Braintree, MA) was advanced from the left femoral artery into the thoracic aorta. For

From the Weil Institute of Critical Care Medicine, Rancho Mirage, CA (MF, MHW, YTC, CC, WT); the Department of Anesthesiology, University Hospital RWTH Aachen, Aachen, Germany (MF); and the Keck School of Medicine, University of Southern California, Los Angeles, CA (MHW, WT).

Presented, in part, at the 2004 Annual Congress of the Society of Critical Care Medicine, but published only as abstracts (7, 8).

Copyright © 2006 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/01.CCM.0000247717.81480.B2

the measurements of right atrial pressure, a 7-Fr, pentalumens, thermodilution-tipped catheter (41216, Abbott Critical Care, Salt Lake City, UT) was advanced from the left femoral vein and flow directed into the pulmonary artery. To induce ventricular fibrillation (VF), a 5-Fr pacing catheter (EP Technologies, Mountain View, CA) was advanced from the surgically exposed right cephalic vein into the apex of the right ventricle. Correct placement of intracardiac catheters was confirmed with the aid of an image intensifier. Because the model of cardiac arrest is characterized by intermittent gasping in which the associated head movement compromises imaging of the sublingual microcirculation, neuromuscular blockade was induced by a bolus injection of 0.2 mg/kg pancuronium 5 mins before inducing VF. The head of the pig was immobilized in a metal harness that was anchored at the temporal bones after local anesthesia with 2% lidocaine.

Experimental Procedures. Cardiac arrest was induced with 1 mA of alternating current delivered to the endocardium of the right ventricle. Mechanical ventilation was discontinued after the onset of VF was confirmed by electrocardiographic and arterial pressure measurements. After 5 mins of untreated VF, precordial compression was started with a pneumatic, piston-driven chest compressor (Thumper 1000, Michigan Instruments, Grand Rapids, MI). Coincident with the start of precordial compression, the animal was mechanically ventilated with a tidal volume of 15 mL/kg and F_{iO_2} of 1.0. Precordial compression was programmed to provide 100 compressions/min and synchronized to provide a compression/ventilation ratio of 5:1, with equal compression-relaxation intervals (i.e., a 50% duty cycle). The compression force was adjusted to decrease the anteroposterior diameter of the chest by 25%. Effects of epinephrine on microcirculatory blood flow were measured after a single bolus injection of 1 mg of epinephrine into the right atrium 1 min after start of precordial compression. After 5 mins of precordial compression, defibrillation was attempted with up to three 150-J biphasic waveform shocks delivered between the right infraclavicular area and the cardiac apex. Failing to reverse VF, 1 min of chest compression preceded delivery of another sequence of up to three shocks. Resuscitation attempts were abandoned after three attempts. If ROSC was achieved with return of mean aortic pressure to ≥ 60 mm Hg that persisted for ≥ 5 mins, the animal was regarded as successfully resuscitated.

Animals were subsequently killed by intravenous injection of 150 mg/kg pentobarbital 5 mins after ROSC. Autopsy was performed to identify any injuries to the bony thorax or the thoracic or abdominal viscera.

Measurements. Dynamic data, including aortic and right atrial pressures, together with the electrocardiogram and the end-tidal CO_2 , were continuously measured and recorded on

a precordial compression-based data-acquisition system, supported by CODAS/WINDAQ hardware/software as previously described (9). CPP was calculated as the pressure gradient between the minimal aortic and coincident right atrial pressure.

The sublingual microcirculation was visualized with the aid of an orthogonal polarization spectral back focus imaging device (CYTOSCAN A/R, Cytometrics, Philadelphia, PA) with a $\times 10$ imaging objective, resulting in an on-screen magnification of $\times 276$. The orthogonal polarization spectral imaging device facilitated visualization of representative fields of the sublingual microcirculation. After removal of gross secretions with gauze, the camera was gently inserted in the mouth of the animal and positioned in the right sublingual fossa at a site approximately 4 cm proximal to the tip of the tongue. Lateral tissue movement was minimized by use of a plastic adapter attached to the optical probe of the orthogonal polarization spectral imaging device, which provided moderate negative pressure such as to retain the objective at a single site without compromise of microcirculatory flow as described by Lindert et al (10). Images were continuously recorded on a conventional video cassette recorder (CT-330 TM, Samsung Electronics America, Secaucus, NJ). Feasibility trials in five animals confirmed the report of Lindert et al. (10) that the negative pressure produced by the plastic adapter did not alter microcirculatory flow under physiologic conditions. Individual recordings of 10 secs in duration were analyzed off-line using a score previously described by Spronk et al. (11), in which 0 represents no flow, 1 represents markedly reduced flow, 2 represents reduced flow, and 3 represents normal flow. This score was calculated for vessels of $< 20 \mu m$ in diameter, representing primarily capillaries (12). Vessel size was mensurated with a micrometer scale superimposed in the video display. Values were obtained at baseline; 0.5, 1, 3, and 5 mins after onset of VF; 1 and 5 mins after start of chest compression; and 1 and 5 mins after ROSC.

Statistical Analysis. All data are presented as mean \pm sp. Normal distribution of the data was confirmed using the Kolmogorov-Smir-

nov test. Analysis of variance was used to establish differences between resuscitated and non-resuscitated animals for microvascular flow in vessels of $< 20 \mu m$ in diameter, CPP, and end-tidal CO_2 at the stated times. Linear correlations were calculated using the Pearson correlation coefficient. A p value of $< .05$ was regarded as statistically significant.

RESULTS

Four of nine animals in the initial group were resuscitated. Microvascular blood flow dramatically decreased within the 0.5-min period that followed the onset of VF in all visualized vessels, followed by a continuous decline. There was progression to absence of flow during the 5-min interval of untreated VF (Fig. 1). Coincident with the start of precordial compression, microcirculatory blood flow was partially restored in each animal. After ROSC, microcirculatory blood flow returned to within 20% of baseline values within 5 mins. In animals that failed resuscitation interventions, significantly lesser increases in capillary flow were measured after 1 min of precordial compression in comparison with resuscitated animals (0.6 ± 0.3 vs. 1.8 ± 0.9 , $p < .05$). After 5 mins of precordial compression, these differences persisted (0.6 ± 0.3 vs. 2.0 ± 0.5 , $p < .01$).

CPP and end-tidal CO_2 decreased during the initial 0.5 min of cardiac arrest, and these decreases paralleled the initial reductions in microvascular blood flow. CPP decreased from 81 to 15 mm Hg and end-tidal CO_2 from 38 to 18 mm Hg immediately after onset of VF. Precordial compression increased CPP and end-tidal CO_2 after 1 and 5 mins to significantly higher values in resuscitated than in non-resuscitated animals, as shown in Table 1, and these increases were again associated with increases in microvascular blood

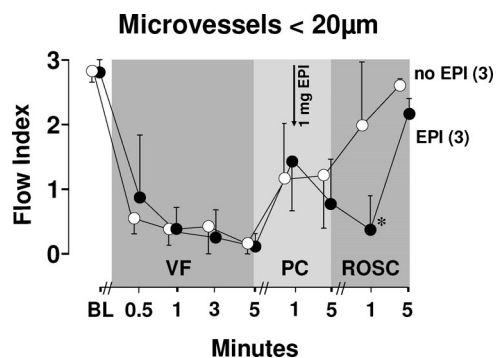


Figure 1. Progression of microvascular blood flow at baseline (BL), during ventricular fibrillation (VF) and precordial compression (PC), and after return of spontaneous circulation (ROSC) when 1 mg of epinephrine (EPI) was administered during PC. * $p < .05$ vs. no EPI.

Table 1. Coronary perfusion pressure (CPP) and end-tidal CO₂ (E_tCO₂) in resuscitated and non-resuscitated animals at baseline, during ventricular fibrillation (VF) and precordial compression (PC), and after return of spontaneous circulation (ROSC)

Timepoint	CPP		E _t CO ₂	
	Resuscitated	Non-Resuscitated	Survivors	Non-Resuscitated
Baseline	89.0 ± 20.2	75.8 ± 6.4	37.0 ± 5.2	37.5 ± 1.3
VF 30	9.7 ± 2.1	9.0 ± 1.6	16.3 ± 4.7	15.5 ± 6.6
VF 60	4.3 ± 2.5	5.5 ± 1.3	15.0 ± 7.0	13.5 ± 8.1
VF 180	4.0 ± 4.6	6.3 ± 6.1	11.3 ± 2.3	13.5 ± 8.7
VF 300	1.7 ± 3.8	4.5 ± 4.2	5.7 ± 4.5	15.8 ± 10.7
PC 60	18.7 ± 4.0	8.7 ± 4.5 ^a	23.3 ± 3.1	10.7 ± 2.1 ^a
PC 300	19.3 ± 3.2	7.3 ± 3.1 ^a	24.3 ± 4.0	11.0 ± 3.5 ^a
ROSC 60	85.7 ± 26.6		49.3 ± 11.7	
ROSC 300	88.3 ± 18.4		44.3 ± 7.4	

^a*p* < .05 vs. resuscitated animals.

flow. Changes in capillary blood flow were highly correlated with CPP (*r* = .82, *p* < .01).

In the second study, changes in microcirculatory blood flow were observed after the onset of VF and the start of precordial compression similar to those in the previous experiment. However, administration of epinephrine resulted in a dramatic and significant decrease in capillary blood flow during the ensuing 4 mins of precordial compression and persisted even when ROSC was achieved, as seen in Figure 1.

Autopsy did not reveal any injury to the bony thorax, the thoracic, or the abdominal viscera in any of the animals.

DISCUSSION

Circulatory shock is predominantly regarded as failure to meet oxygen and energy demands of peripheral tissues and, especially, vital organs. Clinically, diagnosis and treatment of severe circulatory shock is based on invasive hemodynamic measurements of macrocirculatory variables, namely, arterial and venous pressures or flows (13). Ultimately, blood flow, and therefore oxygen delivery, is crucial on the level of the capillary exchange beds, and in recent years, there has been growing evidence that, especially in septic and cardiogenic shock, there is discordance between the macrocirculation and the microcirculation (14, 15). This contrasts with the results of our observations during cardiac arrest and resuscitation, in which there was a close relationship between CPP and capillary flow. Previous studies already suggested but did not prove temporal relationships between the macrocirculation and the microcirculation in this setting

(16–18). Orthogonal polarization spectral imaging proved to be a valuable tool for the real-time assessment of capillary flow in the sublingual mucosa of the pig. Future studies are anticipated to evaluate the effects of various mechanical and pharmacologic interventions on the capillary exchange beds during cardiopulmonary resuscitation. The benefits of epinephrine in the setting of cardiac arrest and resuscitation are discussed controversially. In our experiments, administration of a single bolus of epinephrine resulted in a dramatic decrease in capillary flow and might have compromised tissue blood flow and therefore oxygenation and metabolism. However, the challenge is to simultaneously measure and define threshold levels that guarantee tissue viability. In the present studies, the site of measurement was the sublingual mucosa, reflecting blood flow supplied by the carotid artery, with the implication that such in part reflects the source of cerebral blood flow and therefore potentially brain viability. Ultimately, measurements have to be extended directly to the most important vital organs, namely, the heart and the brain. Our findings might have clinical implications. Both coronary and cerebral circulations are the primary foci for successful resuscitation, and the search continues for objective, noninvasive measurements to secure maximal blood flow during cardiopulmonary resuscitation. End-tidal CO₂ supplies a measurement indicative of pulmonary blood flow and therefore cardiac output. The possibility that visualization of the sublingual microcirculation may guide systemic microvascular flow, including cerebral perfusion, is worthy of further

studies and potentially applicable as a noninvasive option.

We recognize several limitations in the interpretation of our results. We succeeded in improving image quality by minimizing movement artifacts with focus on one field by using a specialized suction device. We cannot exclude the possibility that the procedures themselves may have influenced the microvascular blood flow, especially during extreme low-flow conditions, although the differences between resuscitated and non-resuscitated animals would not be explained by this limitation. Furthermore, use of the semiquantitative score described by Spronk et al. (11) is not an objective measurement. Second, direct translation of our findings in healthy experimental animals during anesthesia and neuromuscular blockade, with the additional use of a metal frame for head immobilization, to human patients—many with underlying cardiovascular disease—cannot be assumed and is a clinically important limitation.

Within these limitations, we conclude that in the experimental setting of cardiac arrest and resuscitation, there is a close connection among macrocirculatory hemodynamics, microvascular flow, and relation to ultimate outcomes. Imaging technologies, such as orthogonal polarization spectral imaging, are feasible methods to accurately visualize the microcirculation in real time. We believe that measurements of microvascular blood flow during cardiac arrest and cardiopulmonary resuscitation will provide additional insights into circulatory mechanisms and serve as a guide to more effective interventions during cardiac arrest and resuscitation.

REFERENCES

1. Kouwenhoven WB, Jude JR, Knickerbocker GG: Closed-chest cardiac massage. *JAMA* 1960; 173:1064–1067
2. Crile GW, Dolley DH: An experimental research into the resuscitation of dogs killed by anesthetics and asphyxia. *J Exp Med* 1906; 8:713–724
3. Paradis NA, Martin GB, Rivers EP, et al: Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990; 263: 1106–1113
4. Fagrell B: The relationship between macro- and microcirculation: Clinical aspects. *Acta Pharmacol Toxicol (Copenh)* 1986; 58(Suppl 2):67–72
5. Groner W, Winkelmann JW, Harris AG, et al:

- Orthogonal polarization spectral imaging: A new method for study of the microcirculation. *Nat Med* 1999; 5:1209–1212
6. Ince C: The microcirculation is the motor of sepsis. *Crit Care* 2005; 9(Suppl 4):S13–S19
 7. Fries M, Tang W, Chang YT, et al: Detrimental effects of epinephrine on microcirculatory blood flow in a porcine model of cardiac arrest. *Crit Care Med* 2004; 32(12 Suppl):A212
 8. Fries M, Tang W, Chang YT, et al: Assessment of microcirculatory blood flow in a porcine model of cardiac arrest. *Crit Care Med* 2004; 32(12 Suppl):A8
 9. Tang W, Weil MH, Noc M, et al: Augmented efficacy of external CPR by intermittent occlusion of the ascending aorta. *Circulation* 1993; 88:1916–1921
 10. Lindert J, Werner J, Redlin M, et al: OPS imaging of human microcirculation: A short technical report. *J Vasc Res* 2002; 39: 368–372
 11. Spronk PE, Ince C, Gardien MJ, et al: Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 2002; 360: 1395–1396
 12. Zweifach BW: Quantitative studies of microcirculatory structure and function: I. Analysis of pressure distribution in the terminal vascular bed in cat mesentery. *Circ Res* 1974; 34:843–857
 13. Pinsky R: Hemodynamic monitoring over the past 10 years. *Crit Care* 2006; 10:117
 14. De Backer D, Creteur J, Dubois MJ, et al: Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. *Am Heart J* 2004; 147:91–99
 15. De Backer D, Creteur J, Preiser JC, et al: Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; 166:98–104
 16. Feher J, Antal M: Ischemic retinal alterations in cardiac arrest. *Ann Ophthalmol* 1979; 11: 909–913
 17. Ginsberg MD, Myers RE: The topography of impaired microvascular perfusion in the primate brain following total circulatory arrest. *Neurology* 1972; 22:998–1011
 18. Lin SR, Korman M: Cerebral circulation after cardiac arrest: Microangiographic and protein tracer studies. *Stroke* 1977; 8:182–188