Coronary Heart Disease

The Application of Oxygen Saturation of Central Venous Blood ($ScVO_2$) in Complicated Acute Coronary Syndrome as a Probable Disease Monitor – A Pilot Study

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Background: The oxygen saturation of the central vein ($ScVO_2$) has been regarded as a surrogate of tissue perfusion in patients of severe sepsis and major surgery. However, $ScVO_2$ in acute coronary syndrome has not been addressed. We tried to delineate the trend of $ScVO_2$ in patients of acute coronary syndrome.

Methods and Patients: This was a prospective observational study in the coronary care unit of a medical center. Patients of acute coronary syndrome with acute lung edema or cardiogenic shock were enrolled. Blood samples from central vein (via 3-lumen catheter in superior vena cava) and peripheral artery immediately after admission, 24 and 48 hours later were analyzed by co-oxymetry method. The primary endpoint was "event-fatality". The secondary endpoint was in-hospital all-cause mortality.

Results: Forty-three patients were enrolled in the period of 3 months. There were 5 event-fatality (event-fatality rate: 11.6%). The non-survivors had lower event-$ScVO_2$ (39.4 ± 12.9%, median 44.5%), while the survivors had higher event-$ScVO_2$ of 65.6 ± 9.9% (median 66.2%) ($p < 0.05$). The APACHE II score (27.8 ± 8.8, median 30.5 vs. 17.4 ± 6.3, median 18, $p < 0.05$) and TISS score (51 ± 22.4, median 51, vs. 44 ± 13.7 median 42.5, $p < 0.05$) showed the same trend. The time series of $ScVO_2$ implicated heterogeneity during the course, but the overall trend showed increment of $ScVO_2$ as the disease improved.

Conclusion: $ScVO_2$ could reflect the disease process of a complicated acute coronary syndrome. It should be one of the integral indices of tissue perfusion in critical patients of primary cardiac events, and it is more practical and accessible than mixed venous oxygen saturation.

Key Words: Acute coronary syndrome • Central vein • Oxygen saturation • $ScVO_2$

INTRODUCTION

Maintaining a balance between the systemic oxygen delivery and oxygen demand is the mainstay in managing the critically ill.[1] However, hemodynamic assessment on the basis of physical examinations, vital signs, central venous pressure[2] and urine output[3] cannot early detect persistent global tissue hypoxia. Parameters used to confirm the balance included mixed venous oxygen saturation (SvO_2), level of arterial lactic acid, etc.[4] SvO_2 has been regarded as a surrogate for the cardiac index, a target in hemodynamic-based therapy.[5] In cases in which the insertion of a pulmonary artery catheter was difficult, venous oxygen saturation could be measured in the central vein.[6] Rivers et al. raised the concept of "early-goal directed therapy" in treating patients with septic shock

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or severe sepsis, by adopting $ScVO_2$ as their primary guide of therapy.[7] However, their study excluded patients of acute coronary syndrome, cardiogenic shock and myocardial infarction. The latest review article described the application of $ScVO_2$ in severe sepsis, septic shock and major surgery.[8] There were few words regarding $ScVO_2$ in acute coronary syndrome and cardiogenic shock. $ScVO_2$ in acute myocardial infarction was ever studied in 1968,[9,10] but it has not been re-evaluated in contemporary coronary care unit. There was little literature discussing the impact of newly-ushered invasive treatment, such as coronary reperfusion therapy, on the changes of $ScVO_2$. Therefore, we tried to conduct a study to examine $ScVO_2$ in the critically ill patients of acute coronary syndrome (ACS).

METHODS AND PATIENTS

Study design

This is a prospective observational study conducted in a 13-bed-based coronary care unit (CCU) of a medium-sized tertiary-care hospital. Any invasive and complex procedures, such as emergent coronary interventions and open-heart surgery, were 24-hour available in this institute. The unit mostly received patients of cardiovascular diseases. But critically ill patients of other medical conditions, such as septic shock or acute respiratory distress, could also be admitted. Informed consent for any necessary invasive procedure and data collection were obtained either from the patient himself/herself or the patient's delegated family member. The study protocol was approved by the institutional review board. Patients of acute coronary syndrome were admitted to the unit, including ST-elevation myocardial infarction (STEMI), non ST-elevation myocardial infarction and unstable angina. The diagnosis of acute coronary syndrome was based on an elevation of myocardial enzymes up to more than 2 times the upper limit that could not be attributable to any other condition, and 1 or 2 of the following parameters: (1) chest pain or dyspnea lasting for more than 30 minutes, and (2) ischemic ECG changes on admission or any later change of ECG caused by acute myocardial infarction. The diagnostic criteria followed the ACC/AHA guidelines.[11,12] The study population only included: 1. patients of "complicated acute coronary syndrome": ST-segment or non-ST segment elevation myocardial infarction of $\geqq$ Killip III; 2. patients of unstable angina presenting with cardiogenic acute lung edema.

The exclusion criteria were: 1. unsuccessful initial resuscitation: refractory hypotension during admission to the unit, which meant unable to maintain mean arterial blood pressure (MAP) above 65 mmHg by any means, indicating failure of initial resuscitation at other sites; 2. disease entities that needed immediate surgical attention; 3. concomitant septic and cardiogenic shock which could not be clearly delineated; 4. patient's or family's unwillingness: those who refused suggested therapy or asked discharge against medical advice; 5. age less than 18 years old; 6. pregnancy; 7. contraindications for central venous catheterization; 8. uncured cancer or any other status of iatrogenic immunosuppressant, such as post-organ transplant, or undergoing chemotherapy.

All of the enrolled patients were graded by APACHE II and TISS score.[13] The patients received cannulation to their superior vena cava with a 3-lumen catheter via either internal jugular, subclavian or supra-clavicular routes on either side. In cases of STEMI who required primary coronary intervention, the cannulation of central vein was performed while awaiting the cath lab crew. For those not demanding primary intervention, the patients received cannulation to the central vein immediately after being admitted to the unit. The position of the catheter was fixed with sutures, and the depth of the tip was verified by chest x-ray or fluoroscope in the cath lab. Blood samples of central vein and peripheral artery were drawn immediately after cannulation and successful resuscitation. Both were sent for analysis of pH value, partial pressure of carbon dioxide ($PaCO_2$/$PcVO_2$), partial pressure of oxygen (PaO_2/$PcCO_2$), content of bicarbonate, base-excess and saturation of oxygen (SaO_2/$ScVO_2$). In addition, the arterial lactic acid was also checked. Two subsequent samples of central venous blood were obtained in the ensuing 24 and 48 hours later (not continuous monitoring), and compared with concomitant arterial blood (co-oxymetry method). The initial oxygen saturation of the central venous blood was termed "event-$ScVO_2$". Accordingly, the event-$ScVO_2$ was obtained immediately after the preliminary and necessary interventions, such as emergent resuscitation, volume replacement, vasopressors or antibiotics via peri-

pheral vascular access.

The primary endpoint was "event-fatality". The "event" meant the primary diagnosis that brought the patient into the intensive care unit. In addition, "event" also referred to any new episodes in the unit that made the patient's hemodynamics compromised or respiration distressed. The "event-survival" was defined as returning to the pre-"event" circumstances, such as free from inotropes or ventilatory support. The secondary endpoint was all-cause mortality in the hospital. Disease-related complications, such as ischemic bowel syndrome after myocardial infarction, were counted in the second endpoint, not the primary one. The clinical data and outcomes were all recorded by an independent study nurse and reviewed by an independent physician. An independent, 3-member external safety, efficacy, and data monitoring committee reviewed interim analyses of the data at regular intervals of one month and recommended that the study be continued or not.

Management of patients

In general, volume replacement was done by adequate crystalloid/colloid supplement, in order to maintain the pressure of the central vein around 10-12 mmHg. The mean arterial blood pressure was maintained above 65 mmHg by intravenous vasopressors, such as dopamine, nor-adrenaline, adrenaline and vasopressin. If the $ScVO_2$ was less than 70%, intravenous dobutamine was added. In the presence of hematocrit less than 30, component therapy with packed red-blood cell was given. Regarding the patients of critical vitals, IABP and ECMO were additional modalities to maintain hemodynamics. The treatment of underlying cardiovascular diseases conformed to the clinical practice guidelines of American College of Cardiolgy/American Heart Association and European Society of Cardiology.[11,12] Echocardiography was performed on all enrollees within 48 hours of admission.

Statistical methods

The baseline characteristics were compared by univariate analysis. Chi-square test was used for categorical variables, and comparison of continuous variables was done by 2-tail *t*-test. A p value of less than 0.05 was considered to indicate statistical significance. The repeated measure ANOVA method was applied to analyze the longitudinal data in SaO_2 and $ScVO_2$ concentration and all analyses were performed in SPSS 11th edition.

RESULTS

From January to April 2006, there were 373 patients admitted to the coronary unit. One hundred and eighty-seven patients were admitted for surgical indications. Of the 186 non-surgical patients, 45 suffered from non-complicated acute coronary syndromes, which meant they were free from any inotropes or respiratory distress. Fifty-four patients were sent to CCU for observation after scheduled coronary interventions. Thirty-four patients were admitted under the primary diagnoses of septic shock and other non-cardiovascular causes. Furthermore, 4 patients' families refused suggested therapy after admission. Six admitted patients poorly responded to initial resuscitations and hence were excluded.

Overall, only 43 patients were enrolled in this study cohort. Table 1 summarized the primary diagnoses, demographics and vital parameters. The patients were put on inotropes (dopamine, dobutamine, nor-adrenaline, adrenaline, or vasopressin) or any means of ventilatory support as indicated. All but two patients among the survivors did not receive percutaneous coronary intervention (PCI) as their coronary anatomy rendered PCI infeasible. There were 44 ACS-related events, as one of the 43 ACS patients experienced two episodes of acute pulmonary edema. There were 5 event-fatality (event-fatality rate: 11.6%), and totally 10 patients passed away in this cohort (all-cause mortality rate: 23.3%). Four of the additional mortalities came from other non-cardiovascular surgical conditions, and the fifth one passed away as her family refused further aggressive treatment after a period of time, during which the $ScVO_2$ was not checked, since the causes of mortality were temporally quite away from the primary event. The causes of mortality are listed in Table 2.

Five patients failed to survive the primary cardiac event. The 5 non-survivors had lower event-$ScVO_2$ (39.4 ± 12.9%, median 44.5%), while the survivors had higher event-$ScVO_2$ of 65.6 ± 9.9% (median 66.2%) ($p < 0.05$) after initial successful resuscitation. The APACHE II score (17.4 ± 6.3, median 18 vs. 27.8 ± 8.8, median 30.5, $p < 0.05$) and TISS score (44 ± 13.7, median 42.5 vs. 51

Table 1. Comparison of the event-survivors and non-survivors

	Survivors: 38 patients (%)	Non-survivors: 5 patients (%)	p value
Age (year-old)	64.5 ± 14.6, median 69	74.3 ± 14.5, median 79.5	< 0.05
Gender (male/female)	25/13	2/3	
Past medical history			
Hypertension	36 (94.7%)	4 (80%)	
Diabetes mellitus	28 (73.7%)	3 (60%)	
Hyperlipidemia	35 (92.1%)	5 (100%)	
Current smoking	27 (71.1%)	2 (40%)	
Cardio/cerebro-vascular disease	12 (31.6%)	2 (40%)	
Diagnosis (%)	STEMI[&]: 24	STEMI: 1	
	Killip III/IV: 18/6	Killip IV: 1	
	Unstable angina/Non-STEMI	Unstable angina/Non-STEMI	
	(Killip III): 14	(Killip III): 4	
Troponin-I > 1 ng/ml	36 (94.7%)	5 (100%)	
LVEF[@] < 45%	30 (78.9%)	4 (80%)	
PCI[$]	36 (94.7%)	5 (100%)	
APACHE II score	17.4 ± 6.3, median 18	27.8 ± 8.8, median 30.5	< 0.05
TISS score	44 ± 13.7, median 42.5	51 ± 22.4, median 51	< 0.05
Initial MAP	72.5 ± 3.2 mmHg	70 ± 5.6 mmHg	NS
Initial serum lactic acid	4.9 ± 0.5 mmol/L	5.2 ± 2.8 mmol/L	NS
Event $ScVO_2$	65.6 ± 9.9%	39.4 ± 12.9%	< 0.05
	median 66.2%	median 44.5%	
Initial mode of oxygen supply			
Mechanical ventilator	27 (71%)	5 (100%)	
NIPPV*	6 (15.8%)		
Simple mask	3 (7.9%)		
Nasal O2 prong	2 (5.3%)		
Initial usage of inotropes (%)	31/38 (81.5%)	4/5 (80%)	
Other mechanical support: No. of patients			
IABP[+]	12 (31.5%)	2 (40%)	
ECMO[#]	2 (5.3%)	0	
Acute medication			
Aspirin	38 (100%)	5 (100%)	
Clopidogrel	38 (100%)	5 (100%)	
Statins	35 (92.1%)	5 (100%)	
Heparin or enoxaparin	38 (100%)	5 (100%)	
Tirofiban	12 (31.5%)	2 (40%)	

[&]STEMI: ST-elevation myocardial infarction. [@]LVEF: left ventricular ejection fraction. [$]PCI: percutaneous coronary intervention. *Non-invasive positive pressure ventilation. [+]Intra-aortic balloon pump. [#]Extra-corporeal membranous oxygenation.

Table 2. Causes of event-fatality and all-cause mortality

Causes of event fatality:	Profound cardiogenic
No. of patients	shock: 5
Additional causes of mortality:	Aortic dissection:1
No. of patients	Major stroke: 1
	Ischemic bowel: 2
	Refuse resuscitation: 1

± 22.4, median 51, $p < 0.05$) both showed differences between the survivors and the non-survivors. In addition, the non-survivors were older (74.3 ± 14.5 year-old, median 79.5) than the survivors. (64.5 ± 14.6 year-old, median 69) ($p < 0.05$). The survivors and non-survivors had similar event-SaO_2 (97.5 ± 3.2% vs 95.2 ± 3.0%, $p > 0.05$), serum lactic acid (4.9 ± 0.5 mmol/L vs. 5.2 ± 2.8 mmol/L, $p > 0.05$) and initial MAP (72.5 ± 3.2 mmHg

vs. 70 ± 5.6 mmHg, $p > 0.05$).

In this series, there were 6 patients who suffered from out-of-hospital cardiac arrest (OHCA) (previously termed as "dead on arrival" DOA). All of them survived and resulted in zero mortality. The initial $ScVO_2$ of the OHCA-patients after initial resuscitation was 64.5 ± 15.1% (median 66.1%), which was significantly higher than in those who failed to survive the primary cardiac event (39.4 ± 12.9%, median 44.5%) ($p < 0.05$).

The time series of SaO_2/$ScVO_2$ of all ACS enrollees are illustrated in Figure 1. The non-survivors mostly passed away within 36 hours after admission and failed to finish the 3rd $ScVO_2$ check, which interrupted the time series. Overall, the survivors bore increasing $ScVO_2$ (69.5 ± 2.5 to 71.4 ± 2.8 to 75.2 ± 2.2%) during the disease course; the trend is depicted in Figure 2.

DISCUSSION

Several biochemical markers have been ushered to predict prognosis of patients of heart failure. The most recently attended one is N-terminal pro-brain natriuretic peptide, which plays as an independent risk predictor in acute cardiogenic pulmonary edema.[14] The biochemical assays, though rapid yielding, could not reflect the patient's condition immediately. And it is impossible to apply these assays as continuous on-line monitor of disease evolution. The value of mixed venous oxygen saturation (SVO_2) has been thoroughly discussed in the literature. The continuous monitoring of this parameter has been suggested as a means to assist the care of the critically ill.[15] However, the acquisition of the mixed venous blood depended upon successful catheterization of the pulmonary artery by Swan-Ganz catheter. However, the risk/benefit relationship is currently being re-evaluated, as recent outcome studies have challenged the routine usage of Swan-Ganz catheter in different scenarios of critical care.[16-19] Therefore, measurement of $ScVO_2$ seems to be an attractive alternative because it can be performed more easily and is less risky.[20] The role of $ScVO_2$ has been thoroughly discussed recently regarding patients of severe sepsis and septic shock.

Our study focused on complicated acute coronary syndrome and cardiogenic shock. Our non-survivors bore $ScVO_2$ less than 50% (39.4 ± 12.9%, median

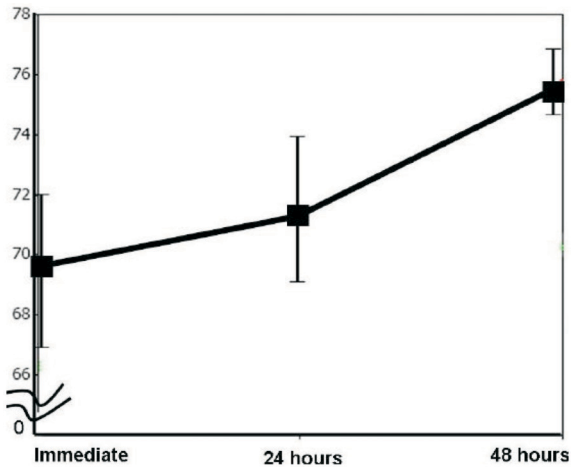
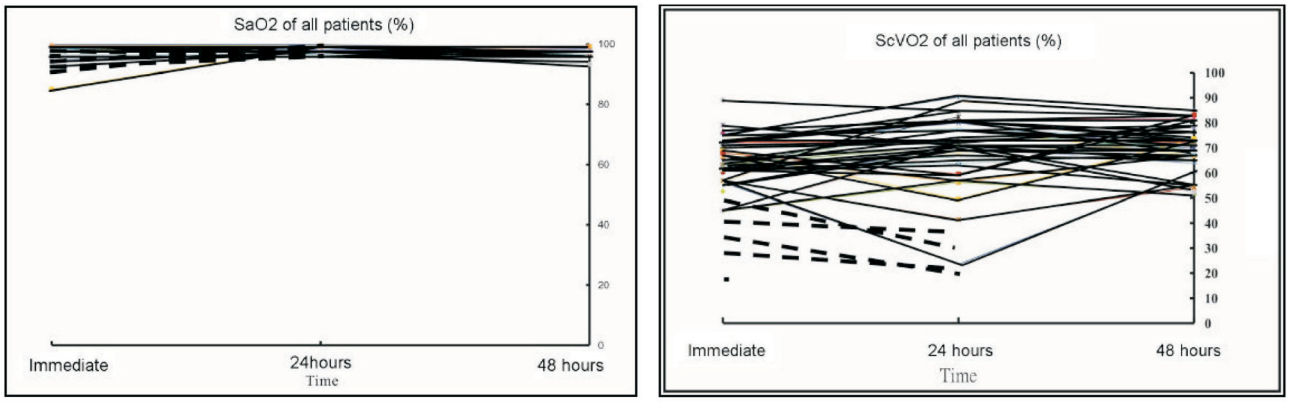


Figure 2. *The trend of time-series of $ScVO_2$ in survivors. The $ScVO_2$ are 69.5 ± 2.5, 71.4 ± 2.8 and 75.2 ± 2.2%, respectively.*



(A) **(B)**

Figure 1. *The time-series of SaO_2 **(A)** and $ScVO_2$ **(B)** of both survivors and non-survivors. The solid lines represent the survivors and show obvious inter-rim heterogeneity with final increment. The bold-dash lines indicate the available data of the non-survivors, and the trend is downward.*

44.5%). Arbitrarily, we might say that extremely low event-$ScVO_2$ (less than 50% in our study) indicated high mortality, while the preserved event-$ScVO_2$ (> 60%) predicted good event-survival. Those patients survived cardiogenic shock, despite severe hypotension, lactic acidosis, and other adverse clinical profiles. In addition, the $ScVO_2$ paralleled APACHE II and TISS scores in predicting outcome. Secondly, the $ScVO_2$ dropped before the manifestation of clinical deterioration in our observation. The phenomenon was observed in several patients of non-ST elevation myocardial infarction, while they were put on early conservative treatment for acute coronary syndrome. The trend is depicted by the Figure 1B, which showed several interim drops of $ScVO_2$ as the disease deteriorated. The $ScVO_2$ recovered after appropriate interventions. In the third place, the $ScVO_2$ in post-MI cardiac tamponade showed very interesting findings. In one patient, the $ScVO_2$ after primary coronary angioplasty was 69%. But it dropped to 49% as cardiac tamponade developed, despite high PaO_2 (> 200 mmHg) and SaO_2 (98%). Interestingly, the $ScVO_2$ returned rapidly to 74% after the tamponade was relieved, while oxygen supplement was being tapered. The change of $ScVO_2$ caused by cardiac tamponade paralleled the hemodynamics, not the arterial oxygenation. Fourthly, the overall time series (by estimated marginal means) of survivors' $ScVO_2$ showed gradual increment as the disease was being remedied. In addition, the time-series also demonstrated interim heterogeneity, which probably meant the alternation of tissue perfusion in the course of acute coronary syndrome.

The above phenomena could be explained by the concept of global tissue oxygenation (in other words "oxygen uptake or consumption", VO_2), which should be maintained as constant as possible by systemic circulation. The main purpose of the constant tissue oxygenation is to maintain the aerobic metabolism in homeostasis. The systemic oxygen consumption/uptake (VO_2) is a function of systemic oxygen delivery (DO_2) and oxygen extraction (the difference of the oxyhemoglobin saturation between the arterial and mixed venous blood, SaO_2-SVO_2). Further, the oxygen delivery (DO_2) depends on cardiac output and the concentration of hemoglobin (Hb), proportionally. In addition, the cardiac output is the result of cardiac stroke volume (SV) times the heart beats per minute (HR). Therefore, the equation of oxygen consumption/uptake could be transformed to $VO_2 = SV * HR * Hb * 13.4 * (SaO_2\text{-}SVO_2)$. The heart rate and hemoglobin have been kept optimal in our patients of acute coronary syndrome (Hb > 10 g/dl, and transvenous pacing if brady-arrhythmia). Therefore, the stroke volume and oxygen extraction become the dominant factors to determine the VO_2. Generally, the stroke volume is mostly attributed to the performance of myocardium. Anything that makes the myocardium malfunction, such as ischemia caused by acute coronary syndrome or cardiac tamponade, will result in decreased stroke volume. In order to maintain constant VO_2 in the face of decreased stroke volume, the oxygen extraction must be augmented. Consequently, the saturation of venous oxyhemoglobin (SvO_2) decreases (the SaO_2 of our patients was kept > 96-98% by any means of ventilatory support). Though $ScvO_2$ has not been regarded as a true substitute for SvO_2, it seems most valuable in identifying trends in the balance between DO_2 and VO_2.[20] That is to say, the $ScVO_2$ dropped as the acute coronary syndrome worsened. On the other hand, the $ScVO_2$ increased, indicating the normalization of tissue oxygen extraction and improved myocardial function, as the acute coronary syndrome resolved. The evolving disease process of acute coronary syndrome, implying varying myocardial performance, explains the heterogeneity of the $ScVO_2$ curves in Figure 1B. The very low $ScVO_2$ in the non-survivors meant that the tissue had extracted maximal oxygen in the face of impaired systemic O_2 delivery, which was attributed to poor performance of the ischemic myocardium. At this stage of very low $ScVO_2$ (< 50% in our study), the tissue had entered the status of global dysoxia, meaning the normal aerobic metabolism failed. High mortality should be inevitable at this moment. On the other hand, the initial $ScVO_2$ could not predict the additional 5 all-cause mortalities (listed in Table 2), which were due to common complications of myocardial infarction. The five additional mortalities came up with initial $ScVO_2$ (65.5 ± 6.1%, median 63.3%), which was similar to the event-survivors' (65.6 ± 9.9%, median 66.2%). There was no further check of $ScVO_2$ during the following complications, since they were not the primary events. As aforementioned, the $ScVO_2$ reflected the status quo of primary cardiac event. The predictive significance of $ScVO_2$ should be limited to the monitored event, and not be extended to other relevant complications.

So far, the central venous oxygen saturation has been adopted as a "goal" to reach in surgical and septic patients. But the application of $ScVO_2$ as an index has been discouraged in the field of cardiogenic shock. The main reason was that $ScVO_2$ could not be used as surrogate for mixed venous O_2 and the two values would never be equivelant.[21,22] However, Dr. Reinhart and Bloos emphasized that $ScVO_2$ should not be used alone in the assessment of the cardiocirculatory system but combined with other cardiocirculatory parameters and indicators of organ perfusion.[10,23] In other words, it was not necessary to regard $ScvO_2$ as a substitute for SvO_2, but $ScVO_2$ could be viewed as one of the integrated parameters representing tissue oxygenation. In our study focusing on complicated acute coronary syndromes, we found that $ScVO_2$ not only paralleled conventional scores of disease severity (APACHE II and TISS), but also sensitively reflected the trend of disease evolution.

Study limitations

This was a single-institute observational study, which has limited significance as inherited. In addition, the scale was rather small, which made receiver's operating curve (ROC) and multi-variable analyses out-of-the-question. Further expansion of the case number is desired in the future, in order to check whether $ScVO_2$ is an independent prognostic parameter. Secondly, the $ScVO_2$ was measured by intermittent co-oxymetry. Maybe this is why we could not observe the "natural course" of $ScVO_2$ in our patients. In the third place, all of the $ScVO_2$ in our study came from the superior vena cava. The impact of different origins of $ScVO_2$ (i.e. superior vena cava, or inferior vena cava) was left unanswered.

CONCLUSION

$ScVO_2$ could reflect the disease process of a complicated ACS. It should be one of the integral indices of tissue oxygenation in critical patients of primary cardiac events. It should be considered that $ScVO_2$ is a valuable tool in identifying trends in the balance between DO_2 and VO_2. In addition, the $ScVO_2$ was a more accessible and practical parameter than SvO_2. In our opinion, the concept of $ScVO_2$ as one of the indices of tissue oxygenation could be applied not only in the field of sepsis but also cardiovascular diseases. Based on the notion of tissue oxygenation, represented by $ScVO_2$, the concept of "early-goal directed therapy" could be probably applied in managing patients of complicated acute coronary syndrome.

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