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Original Article

Point-of-care microcirculation evaluated with sidestream dark field technology: agreement and comparison between sublingual and sublabial mucosa

Jinlong Qu[1*], Minmin Lu[2*], Yueyue Yan[1], Qiuxiang Zhou[1], Wenfang Li[1], Jun Guan[3]

[1]Department of Emergency and Critical Care, Shanghai Changzheng Hospital, Second Military Medical University, Shanghai 200003, China; [2]Department of Anesthesiology, Shanghai Baoshan Traditional Chinese Medicine-integrated Hospital, Shanghai 201999, China; [3]Department of Emergency and Critical Care, Jingan District Zhabei Central Hospital, 619 Zhonghuaxin Road, Shanghai 200070, China. [*]Equal contributors

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Abstract: To investigate whether sublabial mucosa is more suitable for evaluation of microcirculation than commonly used sublingual mucosa in ICU patients, we enrolled 57 adults (47 critically ill patients and 10 volunteers) at convenience from Oct 2018 to Jan 2019. Videomicroscopy images at both sublingual mucosa and sublabial mucosa were acquired at the same time in each enrollee. Qualified images were recorded for later analysis. Four video clips of the same site were comprehensively evaluated to yield one Point Of carE Microcirculation (POEM) score by blinded investigator; POEM scores at both sites were statistically analyzed for correlation and agreement. Procedure time needed to acquire qualified images was also compared. POEM scores between the two sites showed no significant difference and a statistically significant correlation (Spearman correlation coefficient 0.716, $P < 0.001$). The intra-class correlation coefficient was 0.866 (95% C.I. 0.774, 0.921), suggesting good to excellent consistency and agreement between the POEM scores at the two sites. The procedure time needed to acquire 4 clips of qualified images at sublingual and sublabial sites were 10.5±3.9 minutes and 7.1±3.3 minutes respectively, $P < 0.001$. This study indicates that point of care evaluation of microcirculation by POEM score shows good to excellent agreement between sublingual mucosa and sublabial mucosa. It is easier to acquire qualified videomicroscopy images at sublabial mucosa than at sublingual mucosa. Therefore, sublabial mucosa might be more suitable for bedside evaluation of microcirculation with handheld SDF device in ICU.

Keywords: Sidestream dark field, sublabial mucosa, sublingual mucosa, POEM score

Introduction

Microcirculation has been established as an important diagnostic and therapeutic target for treatment in sepsis and other critical illness [1, 2]. Direct visualization of the tissue microcirculation highlights its importance, not only in its overall determination of the severity of microcirculatory dysfunction, but also in the observation of loss of hemodynamic coherence and its types [3-5]. Sublingual microcirculation has been mostly researched in clinical settings since the introduction of direct visualization of tissue microcirculation with the hand-held videomicroscopy [6]. Numerous reports demonstrated that alteration of sublingual microcirculation measured with sidestream dark field (SDF) technology correlated well with outcome and severity of the critical illness [7]. Nevertheless, microcirculation monitoring is currently only recommended for clinical researches rather than routine clinical practice [8, 9]. Two limitations of current technology may deter the popularization and application of the technology in critically ill patients. First, current microcirculatory image analysis needs to be performed offline, which is time and energy consuming. Moreover, it has also subjectivity to some extent [6, 10]. However, real-time evaluation of tissue microcirculation is rather necessary for hemodynamic intervention targeting improvement of tissue perfusion. Therefore, point of care microcirculation assessments have been investigated and validated in several studies, for example

Figure 1. Sublabial mucosa site for placement of SDF device probe.

POC-MFI [11]. The POEM score is a newly established real-time bedside sublingual microcirculatory scoring system. It incorporates two major features of microcirculation-microcirculatory flow and heterogeneity. The authors suggested that POEM score correlates well with microcirculation parameters measured offline with AVA 3.2, such as microvascular flow index (MFI), total vessel density (TVD), perfused vessel density (PVD), proportion of perfused vessels (PPV), De Backer Score (DBS) and microcirculatory heterogeneity index (MHI) [12]. Second, high quality of videomicroscopy images are essential to the accurate interpretation of the microcirculatory measurements. To obtain high quality of image at sublingual area with current SDF technology requires total collaboration or sedation of the patient [1, 13]. Otherwise, the involuntary movements of the patient's tongue often cause pressure artifacts and image drifting, misleading the measurements of microcirculation thereafter [13]. We found in clinical practice that the sublabial mucosa also has abundant microvascular network resembling sublingual mucosa, whereas the SDF device probe is much easier to be stabilized under the lips, making it easier to obtain high quality videomicroscopy images. Therefore, our question in the present study is whether the sublabial mucosa is a more suitable window than the sublingual mucosa to observe the microcirculatory alterations in critically ill patients with the hand-held videomicroscopy device. We hypothesized that the sublabial POEM score is in good agreement with sublingual area by the SDF technique and it is easier to acquire qualified videomicroscopy clips at sublabial mucosa than that at sublingual mucosa.

Methods

Ethical approval

This prospective diagnostic test study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Review Board of Shanghai Changzheng Hospital (No. CZEC2017-08). Written informed consents were obtained from the patients or next of kin.

Study design

This is a self-control study of microcirculation measurements at two different sites in the same patient.

Patients

This study was conducted in a tertiary university hospital from Oct 2018 to Jan 2019. We enrolled both healthy adults and critically ill patients who met the diagnosis criteria of sepsis or septic shock [14] or hypovolemic shock [8] for the purpose of testing our hypothesis in a wider range of microcirculation dysfunction. Patients were excluded from this study if they (1) were in pregnancy; (2) were younger than 18 years old or older than 80 years old; (3) suffered from oral injury; (4) could not cooperate to finish the image sampling procedure. Patients with oral intubation were objectively excluded in this study because of the complicated procedure of image collection at sublingual area.

The TVD, PVD, PPV, DBS, MHI and point of carE microcirculation (POEM) score

We used a Sidestream Dark Field imaging device (Microscan; MicroVisionMedical, Amsterdam, The Netherlands) to acquire sublingual and sublabial microcirculation video clips following manufacturer's instructions. The device was applied gently under the tongue (for sublingual microcirculation) or lips (for sublabial microcirculation; **Figure 1**) without pressure after cleaning the area with gauze. Image col-

Table 1. Patients/volunteers characteristics

Groups	Healthy volunteers	Hemorrhagic shock	Sepsis	Septic shock
Male/female	4/6	12/7	10/4	8/6
Age, yrs	29.8±9.6	46.8±16.4	57.6±16.0	64.1±12.5
SAP (mmHg)	NA	101.0±11.7	119.5±17.8	104.2±24.2
DAP (mmHg)	NA	55.3±11.2	70.7±15.0	56.0±15.6
MAP (mmHg)	NA	70.0±11.6	86.5±14.8	75.2±17.8
HR (bpm)	NA	79.4±14.7	94.5±16.3	93.1±23.0
Lactate (mmol/L)	NA	1.7±1.2	1.3±0.7	2.4±1.7
APACHE II score	NA	4.6±3.5	7.9±4.5	12.6±5.8
SOFA score	NA	1.7±1.8	3.5±2.8	5.4±3.8

NA = not available, SAP = systolic arterial pressure, DAP = diastolic arterial pressure, MAP = mean arterial pressure, HR = heart rate, APACHE = acute physiologic and chronic health evaluation, SOFA = sequential organ failure assessment. SAP, DAP and MAP may be maintained with or without vasopressor.

lection at sublingual area was immediately followed by image collection at sublabial area. The total procedure time usually took less than a half an hour. Therefore, the images at the two sites were collected simultaneously from the clinical point of view. The image quality of the video was required to meet the criteria of the expert consensus [6, 15]. Four clips of at least 5 seconds each from different adjacent areas at both sublingual mucosa and sublabial mucosa were recorded and stored in the device for later evaluation of POEM score. Only those videos with good quality images in terms of illumination, focus, content, brightness, pressure and stability [6] were recorded and stored for later analysis. The TVD, PVD, PPV, DBS, MHI were collected by AVA 3.0. POEM score is a 5-point ordinal scoring system from 1 (worst) to 5 (best), which was designed for bedside evaluation of microcirculation based on hybrid assessment of microcirculatory flow and heterogeneity of 4 individual sublingual or sublabial video microscopy clips from the same person at same time [12]. Briefly, the investigator first comprehensively determines the flow of each of the four clips as (1) Normal; (2) Impaired-Score 2; (3) Critically Impaired-Score 1. Then, only if the flow is normal, the investigator further checked whether heterogeneity is (1) marked-Score 3; (2) mild-Score 4; (3) absent-Score 5. An online tool (http://www.POEMscore.com) for POEM score calculation can be used. All the video clips were acquired by the same investigator but renamed for the purpose of blinding. The procedure times needed for each successful acquisition were recorded. POEM score evaluations were performed offline by another investigator who was blind to patient information and video acquiring sites.

Statistical analysis

All the statistical analyses were performed with SPSS 22 (SPSS Inc., Chicago, IL). The TVD, PVD, PPV, DBS, MHI of sublingual and sublabial mucosa were statistically analyzed for correlation. POEM score difference of no more than 1 between sublingual and sublabial sites was considered as clinically consistent of the two methods. Clinical consistency rate and its 95% confident interval were calculated. The intraclass correlation coefficient (ICC) was used to evaluate the consistency and agreement between sublingual and sublabial POEM [10]. The ICC estimate and its 95% confident intervals were calculated based on a mean-rating (k=2), absolute-agreement, 2-way mixed-effects model. Values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability [10]. Wilcoxon signed-rank test and Spearman's rank correlation coefficient were used to evaluate the difference and correlation between POEMs of the two sites respectively. Paired T test was used for comparison of procedure time between the two sites. A $P < 0.05$ was considered statistically significant.

Results

Totally 57 adults were enrolled in this study at convenience, including 10 healthy volunteers, 14 sepsis patients, 14 septic shock patients and 19 hypovolemic shock patients. There were 34 males and 23 females. The mean age ±

Table 2. Sources of patients

Groups		Etiology	Male	Female
Healthy volunteers	10	NA	4	6
Hemorrhagic shock	19	Gastrointestinal hemorrhage	7	7
		Traumatic hemorrhage	5	0
Sepsis	14	Pancreatitis	3	1
		Pneumonia	7	3
Septic shock	14	Diabetic foot	1	1
		Pneumonia	7	1
		Abdominal infection	0	4

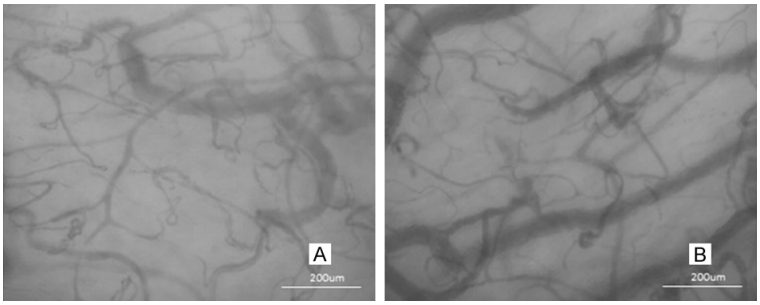

Figure 2. Representative images of sublingual (A) and sublabial (B) microcirculation.

standard deviation (SD) was 50.8±18.3 years. **Table 1** demonstrated the characteristics of the patients and healthy volunteers at the time of investigation. The etiologies of hypovolemic shock, sepsis, septic shock are shown in **Table 2**.

In this study, the microvessels in sublabial mucosa nearby labial frenulum are in almost the same pattern with those in sublingual area (**Figure 2**). TVD, PVD, PPV, DBS, MHI of sublingual and sublabial mucosa showed a linear correlation ($P < 0.01$), TVD and PVD of sublingual mucosa was strongly correlated to sublabial mucosa (r=0.872, 0.819), and PPV, DBS, MHI of sublingual mucosa was correlated to sublabial mucosa (r=0.557, 0.550, 0.579) (**Figure 3**).

And both of the median (25%, 75% percentile) of sublingual and labial POEM scores were 4.0 (3.0, 4.0). Wilcoxon signed-rank test showed P=0.194, suggesting that there was no statistically significant difference between POEM scores at the two sites. **Table 3** is the frequency table by POEM scores at the two sites. From this table, the concordance rate between POEM scores at the two sites was calculated as 98.2% (95% C.I. 94.7%, 100%). The Spearman correlation coefficient between the POEM scores at the two sites was 0.716, $P < 0.001$. The ICC was calculated as 0.866 (95% C.I. 0.774, 0.921), suggesting good to excellent consistency and agreement between the POEM scores at the two sites. The procedure time needed to acquire good quality video-microscopy clips with SDF technology at sublingual and sublabial sites were 10.5±3.9 minutes and 7.1±3.3 minutes respectively, $P < 0.001$ (**Table 3**).

Discussion

Our major findings in the present study are that (1) POEM scores by hand-held SDF imaging device at sublabial mucosa are in good to excellent agreement with those at sublingual mucosa. (2) Acquiring good quality SDF image at sublabial mucosa requires less time than that at sublingual mucosa. To the best of our knowledge, this is the first report to compare the correlation and agreement between sublingual and sublabial microcirculation.

Sublingual mucosa has been the site of microcirculatory measurements using a handheld SDF device in most clinical studies. However, acquiring high-quality SDF images at sublingual area is still a difficult task, mainly due to image drifting caused by involuntary movement of the patient's tongue and instability of device probe due to lack of ideal fulcrum. In addition, the depth of probe placement in the sublingual area is difficult to fine-tune, therefore focus and pressure have become another two important factors affecting the image quality. Without qualified images, microcirculation analysis and interpretation would cause confusion.

In the present study, we found that it was much easier to acquire good quality images at sublabial site with the handheld SDF device. When the SDF device probe is gently placed between the sublabial mucosa and the gums, the front part of the probe gently but firmly rests on the gums, greatly reducing the movement of the

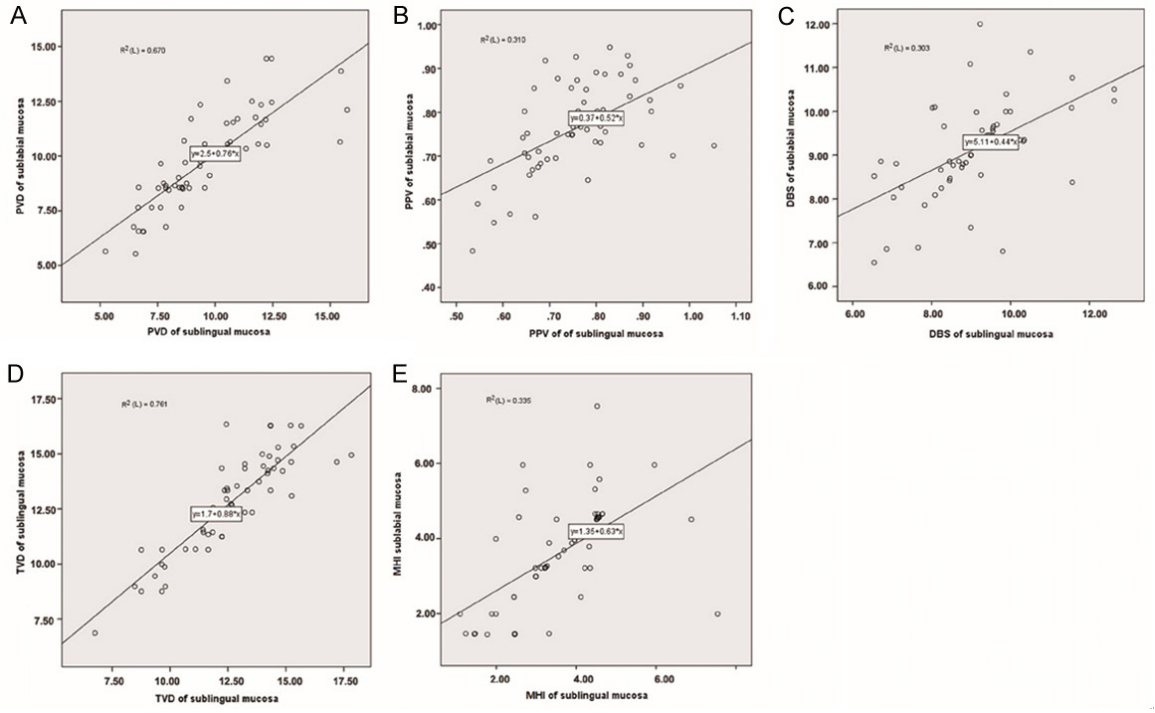

Figure 3. Correlation of sublingual and sublabial TVD, PVD, PPV, DBS, HI. TVD of sublingual mucosa was strongly correlated to sublabial mucosa (r=0.872), P=0.000, y=1.7+0.88x (x: sublingual mucosa TVD, y: sublabial mucosa TVD). PVD of sublingual mucosa was strongly correlated to sublabial mucosa (r=0.819), P=0.000, y=2.5+0.76*x (x: sublingual mucosa PVD, y: sublabial mucosa PVD). PPV of sublingual mucosa was correlated to sublabial mucosa (r=0.557), P=0.000, y=0.37+0.52x (x: sublingual mucosa PPV, y: sublabial mucosa PPV). The sublingual DBS was correlated to sublabial mucosa (r=0.550). P=0.000, y=5.11+0.44*x (x: sublingual mucosa DBS, y: sublabial mucosa DBS). MHI of sublingual mucosa was correlated to sublabial mucosa (r=0.579). P=0.000, y=1.35+0.63x (x: sublingual mucosa MHI, y: sublabial mucosa MHI).

Table 3. Frequency table by sublingual and sublabial POEM scores

		Sublabial POEM score					Total
		1	2	3	4	5	
Sublingual POEM score	1	2	0	0	0	0	2
	2	0	4	3	0	0	7
	3	0	2	2	9	0	13
	4	0	1	1	17	5	24
	5	0	0	0	5	6	11
Total		2	7	6	31	11	57

probe. At the same time, neither the upper lip nor the lower lip would move by itself. Therefore, the relative position between the SDF device probe and the sublabial mucosa would remain essentially fixed. Moreover, the placement depth of the SDF probe and whether it creates pressure on the sublabial mucosa can be easily observed from outside. And also due to the improved stability of the probe, it is easy to finely adjust the placement depth and even the pressure on the microvessels beneath the mucosa.

We also observed in this study that the microvessels in sublabial mucosa nearby labial frenulum are in almost the same pattern with those in sublingual area. This may be explained by the same embryologic origin and the anatomical closeness between the two sites. This study implicated that POEM scores of sublabial microcirculation and sublingual microcirculation are highly consistent in bedside monitoring and are therefore interchangeable.

We chose POEM score in the present study as a real-time evaluation tool for sublingual or sublabial microcirculation. Previous studies mostly used parameters such as MFI, PPV, PVD, MHI to reflect the status of sublingual microcirculation [16-18]. The acquisition of these param-

eters only relies on offline analysis based on Automated Vascular Analysis (AVA) software, which is the current gold standard of microcirculation analysis. However, the offline analysis is time consuming and operator dependent. To make instant clinical decisions targeting improvement of microcirculation in critically ill patients, rapid bedside tool of evaluation is essential. POEM score is a newly developed tool for evaluation of sublingual microcirculation. Although POEM score is a kind of subjective visual evaluation, it has been shown to correlate well with the parameters measured by traditional offline computer analysis, such as PVD, PPV, MHI and MFI [12]. It has also to be shown to work well in a recently published paper [19].

There are several limitations in this study. First, in this study, we used point of care evaluation tool of microcirculation to mimic the real clinical world. However, the nature of this subjective assessment determines that its measurement is not as accurate as traditional computer analysis. Second, The POEM score does not include the assessment of vessel density [12]. The difference and agreement between sublingual microvessel density and sublabial microvessel density are needed to be further investigated. However, POEM score did correlate well with perfused vessel density [12], which is the interest of our evaluation. Finally, this is a single center study including a relatively small number of patients.

In conclusion, point of care evaluation of microcirculation by POEM score shows good to excellent agreement between sublingual mucosa and sublabial mucosa. It is easier to acquire qualified videomicroscopy images at sublabial mucosa than at sublingual mucosa. Sublabial mucosa is more suitable for bedside evaluation of microcirculation with handheld SDF device in ICU.

Disclosure of conflict of interest

None.

Address correspondence to: Jun Guan, Department of Emergency and Critical Care, Jingan District Zhabei Central Hospital, 619 Zhonghuaxin Road, Shanghai 200070, China. Tel: +86-13611777540; E-mail: drguanjun@hotmail.com

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