Prolonged observation time reveals temporal fluctuations in the sublingual microcirculation in pigs given arginine vasopressin

Anders Benjamin Kildal,1,3 Thor Allan Stenberg,2,3 Espen Sanden,1 Truls Myrmel,2,3 and Ole-Jakob How1
1Cardiovascular Research Group, Department of Medical Biology, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway; 2Cardiovascular Research Group, Department of Clinical Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway; 3Department of Cardiothoracic and Vascular Surgery, Heart and Lung Clinic, University Hospital of North Norway, Tromsø, Norway

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Prolonged observation time reveals temporal fluctuations in the sublingual microcirculation in pigs given arginine vasopressin. J Appl Physiol 118: 965–970, 2015. First published February 12, 2015; doi:10.1152/japplphysiol.00900.2014.—Intravital videomicroscopy of sublingual microcirculation is used to monitor critically ill patients. Existing guidelines suggest averaging handheld video recordings of ~20 s in duration from five areas. We assessed whether an extended observation time may provide additional information on the microcirculation. Pigs (n = 8) under general anesthesia were divided between two groups, one with manually held camera, in which microcirculation was assessed continuously for 1 min in five areas, and one with a fixed camera, in which the observation time was extended to 10 min in a single area. The microcirculation was challenged by infusing arginine vasopressin (AVP). In the fixed group, ischemic acute heart failure was induced by left coronary microembolization, and the AVP infusion was repeated. All recordings were divided into 20-s sequences, and the small-vessel microvascular flow index (MFI) was scored and averaged for each measurement point. When administering 0.003, 0.006, and 0.012 IU·kg⁻¹·min⁻¹ of AVP, we observed that the small-vessel MFI in the fixed 10-min group was significantly reduced (2.03 ± 0.38, 0.98 ± 0.18, and 0.48 ± 0.11) compared with both the initial 20 s (2.77 ± 0.04, 2.06 ± 0.04, and 1.74 ± 0.06; P < 0.05) and the 1-min total (2.63 ± 0.09, 1.70 ± 0.07, and 1.33 ± 0.16; P < 0.05) in the handheld group. In acute heart failure, the cardiac output decreased to half of the preischemic values. Interestingly, the small-vessel MFI was more affected by the administration of 0.001 and 0.003 IU·kg⁻¹·min⁻¹ of AVP in acute heart failure (1.62 ± 0.60 and 1.16 ± 0.38) compared with preischemic values (2.86 ± 0.09 and 2.03 ± 0.38; P < 0.05). In conclusion, a prolonged recording time reveals temporal heterogeneity that may impact the assessment of microcirculatory function.

microcirculation; flowmotion; sidestream dark field imaging; arginine vasopressin; acute heart failure

THE SUBLINGUAL MICROCIRCULATION has been extensively studied over the last decade, mainly because it is easily accessible in humans and by the introduction of commercial handheld intravital videomicroscopes [i.e., orthogonal polarization spectral (10) and sidestream dark-field (SDF) (9) imaging devices]. According to the existing guidelines, the image acquisition should include high-quality sequences from three to five different sublingual areas of at least 20 s in duration each (5). Using this approach, an impaired sublingual microcirculation has been demonstrated in both sepsis (4) and cardiogenic shock (3). However, experienced users have claimed difficulty in obtaining stable handheld recordings for longer than 10 s without pressure artifacts in human subjects (1). Interestingly, applying a surrounding image-acquisition stabilizer and fixing the SDF probe to a mechanical arm can extend the duration of stable recordings (1).

Short recordings might be disadvantageous because a longer observation time with intravital videomicroscopy has been shown to reveal reproducible, time-wise microcirculatory fluctuations in experimental sepsis (14), hemorrhage (26), and flow-reduction (18) models. Such temporal fluctuations are not always limited to the capillaries but may also appear in other vessels of the microcirculation (28). Importantly, temporal fluctuations in venule blood flow could potentially cause selection bias because the existing guidelines state that at least one perfused venule should be observed in the field to ensure that no pressure artifacts are introduced by the camera (5).

To our knowledge, temporal fluctuations in the sublingual microcirculation have not been described in detail. In the present study, we obtained recordings of the sublingual microcirculation using an SDF probe attached to a mechanical arm that was fixed to a single sublingual area for the entire experiment to extend the microcirculatory observation period. Ten-minute recordings were compared with the guideline recommendation of handling intermittent recordings ~20 s in duration from several different areas to assess whether the extended recordings revealed important fluctuations missed in the standard setup. To address the physiological response over time, we used a clinically relevant pig model, in which the microcirculatory function was altered by infusing a potent vasoconstrictor (arginine vasopressin, AVP), and a low cardiac output state was induced by acute myocardial ischemia. We hypothesized that a prolonged recording time with a fixed camera is superior in detecting important microcirculatory changes compared with the guideline assessment.

MATERIALS AND METHODS

The experimental protocol was approved by the local steering committee of the Norwegian Animal Research Authority and was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Eight castrated male domestic pigs (Norwegian Landrace, Yorkshire, and Duroc hybrids) weighing 32 ± 2 kg were adapted to the animal facilities for 4–7 days and fasted overnight (with free access to water) before the experiment. 

Anesthesia and surgical preparation. The animals were premedicated intramuscularly with 20 mg/kg ketamine, 0.5 mg/kg midazolam, and 0.03 mg/kg atropine. Isoflurane was administered during endo-
tracheal intubation, and the animals were ventilated with a volume-controlled ventilator and a positive end-expiratory pressure of 5 cmH2O (Servo 900 D, Elema-Schönander). The ventilator settings were adjusted according to capnography and repeated arterial blood gas sampling (10–13 kPa PaO2, 5–6 kPa PetCO2, and PaCO2). General anesthesia was induced with 0.01 mg/kg fentanyl and 10 mg/kg pentobarbital sodium through an ear vein and was maintained with 0.02 mg·kg−1·h−1 fentanyl, 4 mg·kg−1·h−1 pentobarbital sodium, and 0.3 mg·kg−1·h−1 midazolam through a central venous catheter. The circulating volume was maintained by a 10 ml·kg−1·h−1 infusion of 0.9% NaCl supplemented with 1.25 g/l glucose. Heparin (2,500 IU) and 150 mg amiodarone were administered to prevent catheter clotting and malignant arrhythmias. A normal core temperature was maintained at 38°C using a thermal mattress. Introducer sheaths were placed in the external jugular veins and femoral arteries to facilitate the following vascular recordings and interventions: 1) measurements of central venous pressure, mean pulmonary artery pressure, cardiac output, mixed venous O2 saturation, and core temperature via a 5-Fr Swan Ganz catheter (Edvard Lifesciences) inserted in the pulmonary artery through the left external jugular vein; 2) mean arterial pressure measurements and arterial blood sampling through an aortic catheter; and 3) left coronary artery catheterization for microembolization and induction of acute ischemic heart failure in a subset of the pigs. A 10-Fr suprapubic catheter was used to drain the urinary bladder.

**Experimental protocol.** Following surgery and a 30-min stabilization period, the animals were randomized to microvascular assessment using either a handheld device for 5 × 1 min (n = 4) or the device affixed to a mounted stabilizer for 1 × 10 min (n = 4). Complete data sets with hemodynamics, temperature, blood samples, and microcirculatory recordings were collected at all of the measurement points. Following baseline recordings, AVP was administered for 20 min before any new measurements were obtained. Subsequently, AVP was administered in intervals with each dose followed by microcirculatory recordings after reaching a hemodynamic steady state. The following AVP doses were used: 0.001, 0.003, 0.006, and 0.012 IU·kg−1·h−1. AVP was withdrawn, and, after 100 min of washout, new recordings were acquired. In the fixed 1 × 10 min group, the main trunk of the left coronary artery was subsequently catheterized with a 4-Fr angiographic catheter under fluoroscopic guidance, and coronary microembolization was performed using 50-μm polystyrene microspheres (Chromosphere, Duke Scientific) dissolved in 0.9% sodium chloride and 0.01% Tween 80 (25). The degree of contractile dysfunction was titrated to a 30% decrease in cardiac output through repeated injections of 10–15 mg of microspheres every 5–10 min. After the induction of acute heart failure, a new baseline recording and a complete set of AVP measurements were repeated using the same protocol as in the preischemic recordings (Fig. 1).

**Microcirculatory video recordings.** The microcirculation was evaluated using an SDF imaging device with a ×5 objective lens (Microscan, Microvision Medical). Briefly, six light-emitting diodes (LEDs) concentrically placed around the central microscope objective provided pulsed illumination in synchrony with the recording frame rate (25 frames/s). The central wavelength of the LEDs was 530 nm, which is the wavelength of an isosbestic point in the absorption spectra of deoxy- and oxyhemoglobin, ensuring optimal absorption by hemoglobin in the red blood cells (RBCs) (9). Importantly, because only hemoglobin absorbs this wavelength, only the vessels containing RBCs are discernible. At each measurement point in the handheld 5 × 1 min group, steady handheld recordings lasting 1 min were obtained from five sublingual areas, with careful avoidance of pressure artifacts by ensuring that venular flow was present throughout the duration of the recording (5). In the fixed 1 × 10 min group, the SDF device was attached to a custom-made flexible arm, with a micrometer screw allowing for precise adjustment of the SDF probe relative to the sublingual tissue. After an area was selected for image recordings of the sublingual mucosa (by agreement of 2 investigators), the SDF probe was placed ~5 mm above the area of interest using the flexible arm, at which point the arm was fixed and the probe was moved by the micrometer screw until it made contact with the sublingual tissue. The SDF probe was fixed in this position throughout the experiment. In the fixed 1 × 10 min group, the sublingual microcirculation was recorded continuously for 10 min at each measurement point. The SDF images were recorded electronically for offline analysis.

**Microcirculatory video analysis.** Image analysis was conducted using a commercially available software package (Automated Vascular Analysis, Microvision Medical). Vessels were separated into small and large vessels using 20 μm as the cutoff in accordance with established protocols (5). Small-vessel flow was classified using the microvascular flow index (MFI) (5, 24). This score is based on the determination of the predominant type of flow in four quadrants of the recorded images. The flow was characterized in the range between 0 (no flow) and 3 (flow). In the handheld 5 × 1 min group, 1-min recordings at each measurement point were divided into 20-s segments. The MFI was scored for each 20-s period, and MFIs from five different sublingual areas in each animal were averaged for the initial 20 s and for the 1-min total. In the fixed 1 × 10 min group, continuous 10-min recordings were divided into 20-s segments. The MFI was scored for each 20-s segment and then was averaged for each measurement point in each animal. In one pig from the 1 × 10 min group, large-vessel MFI was also assessed when infusing a high dose of AVP (Fig. 4, Supplemental Video S1; supplemental material for this article is available online at the Journal of Applied Physiology website). The spatial flow heterogeneity index (27) was calculated in the handheld group for the initial 20 s. This value was calculated as the highest site MFI minus the lowest site MFI divided by the mean MFI across all of the sublingual sites in a given animal. To determine the temporal heterogeneity in the fixed group, we calculated the highest time MFI minus the lowest time MFI divided by the mean MFI during the 10-min recording. This value was called the temporal flow heterogeneity index.

**Statistics.** The hemodynamic data are presented as means ± SD, whereas microcirculatory data are presented as means ± SD and as scatter plots. The hemodynamic and microcirculatory data were analyzed using a linear mixed-model approach with a restricted maximum likelihood method and the subject identifier as the random effect. Within trends of preischemic or acute heart failure, measurements that were not identified as significant by linear mixed-models were also assessed by one-way repeated-measure ANOVA. P values were adjusted for multiple comparisons using Tukey’s test; P < 0.05 was considered statistically significant, and all analyses were conducted in JMP 9.0 (SAS Institute).
RESULTS

**Effects of AVP on microcirculatory parameters in both groups.** There was no difference in mean small-vessel MFI between the 5 × 1 min group and the 1 × 10 min group at both the baseline and the post-AVP measurement. All groups demonstrated a decrease in mean small-vessel MFI when we administered 0.003–0.012 IU·kg⁻¹·min⁻¹ AVP (Fig. 2). After administering 0.006–0.012 IU·kg⁻¹·min⁻¹ AVP, we detected a greater reduction in mean small-vessel MFI by the 1-min group and the 1-min total recordings compared with both the initial 20-s and 1-min total recordings in the 5 × 1 min group when we administered 0.003–0.012 IU·kg⁻¹·min⁻¹ AVP.

**Effects of AVP in acute heart failure in the fixed 1 × 10 min group.** Following coronary microembolization in the 1 × 10 min group, acute heart failure was evident, with reductions in stroke volume and cardiac output and an increase in the systemic oxygen extraction ratio. With incremental AVP doses during acute heart failure, the systemic vascular resistance was significantly less than preischemic values when reaching the highest AVP dose (Table 1). The mean small-vessel MFI was significantly more reduced when we administered 0.001–0.003 IU·kg⁻¹·min⁻¹ AVP during acute heart failure compared with preischemic values (Fig. 3A). Notably, minor variations in single MFI values appeared similar between baseline and the post-AVP measurements, demonstrating that temporal microcirculatory changes were reversible after the discontinuation of AVP. Furthermore, this reversibility was observed with both preischemic and acute heart failure recordings (Fig. 3B).

**Recordings from one experiment are shown in the Supplemental Video S1** and in Fig. 4, demonstrating the typical major temporal microcirculatory fluctuations revealed during AVP infusion.

**Table 1. Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0.001</th>
<th>0.003</th>
<th>0.006</th>
<th>0.012</th>
<th>Post-AVP</th>
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<tr>
<td><strong>Mean arterial pressure, mmHg</strong></td>
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<tr>
<td>Preischemic</td>
<td>78 ± 8</td>
<td>85 ± 9</td>
<td>88 ± 10†</td>
<td>92 ± 14†</td>
<td>96 ± 16†</td>
<td>76 ± 7</td>
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<tr>
<td>Acute heart failure</td>
<td>62 ± 10</td>
<td>65 ± 9</td>
<td>71 ± 9</td>
<td>77 ± 13*</td>
<td>75 ± 16</td>
<td>62 ± 15</td>
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<tr>
<td><strong>Mean pulmonary artery pressure, mmHg</strong></td>
<td></td>
<td></td>
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<tr>
<td>Preischemic</td>
<td>23 ± 3†</td>
<td>23 ± 2†</td>
<td>23 ± 2†</td>
<td>24 ± 2†</td>
<td>25 ± 2†</td>
<td>27 ± 3*</td>
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<tr>
<td>Acute heart failure</td>
<td>33 ± 4§</td>
<td>36 ± 2§</td>
<td>36 ± 3§</td>
<td>38 ± 4§</td>
<td>37 ± 7§</td>
<td>39 ± 5§</td>
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<td><strong>Central venous pressure, mmHg</strong></td>
<td></td>
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<tr>
<td>Preischemic</td>
<td>10 ± 1†</td>
<td>11 ± 1†</td>
<td>12 ± 1†</td>
<td>13 ± 1†</td>
<td>13 ± 1†</td>
<td>9 ± 1*</td>
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<tr>
<td>Acute heart failure</td>
<td>11 ± 1‡</td>
<td>12 ± 1</td>
<td>13 ± 1</td>
<td>13 ± 1*</td>
<td>14 ± 1*</td>
<td>12 ± 1§</td>
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<td><strong>Cardiac output, l/min</strong></td>
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<tr>
<td>Preischemic</td>
<td>3.8 ± 0.5†</td>
<td>2.9 ± 0.5†</td>
<td>2.6 ± 0.5†</td>
<td>2.3 ± 0.4†</td>
<td>2.2 ± 0.2*</td>
<td>5.0 ± 0.4*</td>
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<tr>
<td>Acute heart failure</td>
<td>2.6 ± 0.2§</td>
<td>2.3 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.3*</td>
<td>1.9 ± 0.4*</td>
<td>2.6 ± 0.5§</td>
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<td><strong>Heart rate, beats/min</strong></td>
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<tr>
<td>Preischemic</td>
<td>71 ± 5†</td>
<td>60 ± 7†</td>
<td>56 ± 7†</td>
<td>54 ± 7†</td>
<td>54 ± 7†</td>
<td>89 ± 8*</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>104 ± 12§</td>
<td>101 ± 7§</td>
<td>99 ± 8§</td>
<td>99 ± 18§</td>
<td>103 ± 17§</td>
<td>125 ± 22§</td>
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<tr>
<td><strong>Stroke volume, ml/beat</strong></td>
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<tr>
<td>Preischemic</td>
<td>53 ± 6</td>
<td>48 ± 6*†</td>
<td>47 ± 7†</td>
<td>44 ± 6*†</td>
<td>42 ± 4*†</td>
<td>57 ± 3</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>25 ± 2§</td>
<td>23 ± 3§</td>
<td>22 ± 2§</td>
<td>21 ± 4§</td>
<td>19 ± 5§</td>
<td>22 ± 6§</td>
</tr>
<tr>
<td><strong>Systemic vascular resistance, dyn·s·cm⁻²</strong></td>
<td></td>
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<tr>
<td>Preischemic</td>
<td>1,466 ± 283</td>
<td>2,044 ± 322†</td>
<td>2,374 ± 385†</td>
<td>2,733 ± 485†</td>
<td>3,022 ± 600†</td>
<td>1,082 ± 164</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>1,606 ± 335</td>
<td>1,882 ± 409</td>
<td>2,210 ± 409§</td>
<td>2,540 ± 509§</td>
<td>2,569 ± 393†§</td>
<td>1,514 ± 281</td>
</tr>
<tr>
<td><strong>Systemic oxygen extraction ratio</strong></td>
<td></td>
<td></td>
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<tr>
<td>Preischemic</td>
<td>0.47 ± 0.05†</td>
<td>0.55 ± 0.06*†</td>
<td>0.59 ± 0.07*†</td>
<td>0.60 ± 0.07*†</td>
<td>0.62 ± 0.07*†</td>
<td>0.36 ± 0.05*</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>0.64 ± 0.09§</td>
<td>0.71 ± 0.08§</td>
<td>0.72 ± 0.05§</td>
<td>0.75 ± 0.07§</td>
<td>0.75 ± 0.09§</td>
<td>0.69 ± 0.09§</td>
</tr>
</tbody>
</table>

Arterial lactate, mmol/l |          |       |       |       |       |           |
| Preischemic            | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.8 ± 0.3 | 1.2 ± 0.5*† | 1.7 ± 0.8*‡ | 0.6 ± 0.2 |
| Acute heart failure    | 0.6 ± 0.3 | 0.7 ± 0.3 | 0.9 ± 0.2 | 1.2 ± 0.5* | 1.6 ± 0.7* | 0.9 ± 0.3 |

Data are presented as means ± SDs. Hemodynamics during preischemic (n = 8) and acute heart failure measurements (n = 4). Systemic oxygen extraction ratio was calculated as the difference between arterial oxygen saturation and mixed venous saturation. *P < 0.05 within preischemic or acute heart failure measurements compared with baseline. †P < 0.05 within preischemic or acute heart failure measurements compared with prearginine vasopressin (AVP) measurement. ‡P < 0.05 between the baseline measurement in acute heart failure and the preischemic post-AVP measurement, and §P < 0.05 between the preischemic and acute heart failure measurements.
DISCUSSION

The main observation of this study is that both handheld and fixed setups detect important microcirculatory alterations caused by vasopressor treatment. An extended recording time also reveals temporal fluctuations that may impact the microcirculatory assessment. Furthermore, this study demonstrates that AVP acts more potently as a vasoconstrictor in a systemic low-flow state compared with normal flow and thus has potential to act as a pharmacological marker of an unstable microcirculation.

Major temporal fluctuations in RBC velocity with a frequency of \( \leq 3 \) cycles/min in the microcirculation are defined as slow-wave flowmotion (SWFM) (18) and are generated by dynamic fluctuations in vessel diameter (i.e., vasomotion) in the proximal arterioles (20). SWFM may occur in the skin during normal conditions (12, 21). In muscle, SWFM has been seen following changes in local perfusion conditions (18). Thus an extended observation period is needed to characterize the mean tissue perfusion properly. In our model, SWFM expressed by the temporal heterogeneity of sublingual MFI was induced by an AVP infusion using clinically relevant doses (Fig. 4). These results were compatible with observations from a dose-response experiment using AVP in a healthy, awake hamster window-chamber preparation (7).

Fig. 3. Effects of AVP in acute heart failure in the fixed 1 × 10 min group. A comparison of the small-vessel MFI before and after induction of acute heart failure in the fixed 1 × 10 min group. The data are presented as the mean small-vessel MFI for each individual recording in A and as all individual small-vessel MFI assessments in B. ○, preischemic measurements; ●, acute heart failure measurements. \( \$P < 0.05 \) between the preischemic values and acute heart failure values.

Fig. 4. Typical 10-min recording of a single small- and large-vessel MFI assessment when infusing AVP. Time-wise fluctuations are seen in both small and large vessels during AVP infusion, revealing that slow-wave flowmotion could appear in the sublingual microcirculation.
The AVP response is of particular interest in low-flow states with reduced tissue perfusion. AVP is part of the physiological response in extreme hypotension and in clinical syndromes of heart failure (13). In addition to its fluid retention effect (2), AVP acts as a potent vasoconstrictor in these pathophysiological states (11, 15). Using AVP as a pharmacological compound in low-flow states, it is possible to assess the receptiveness of the microcirculation in a particular pathophysiological setting.

The threshold dose of AVP required to induce SWFM could be influenced by two main factors: 1) AVP-induced decline in cardiac output (Table 1), thereby reducing the local blood flow (15); and/or 2) the local vasoconstrictive effect of AVP on the sublingual microcirculation. In our study, we observed that the microcirculation was more sensitive to AVP infusion following myocardial ischemia, which was evident because SWFM occurred at a lower AVP dose in acute heart failure compared with preischemic values. To our knowledge, no study has investigated local vasoconstrictive effects of AVP in a low-flow condition. In a canine study (29) evaluating SWFM during hemorrhagic hypotension, a pharmacologically induced vasoconstrictive threshold was assessed by topical application of epinephrine to the microcirculatory area of interest. Similar to our observation, the authors observed that the local vasoconstrictive effect of epinephrine is more potent in a low-flow condition compared with normal flow.

SWFM is a relevant parameter when using laser Doppler flowmetry (LDF) because of easier recording and analysis of temporal data. LDF is based on frequency shift in light beams scattered by moving RBCs, and it provides an average digital signal of RBC flow in all vessels of the tissue sample investigated (16). In an LDF study investigating SWFM attributable to reduced blood flow, local denervation abolished SWFM, whereas an infusion of AVP at a given dose restored SWFM (22). Interestingly, the same dose of AVP with normal blood flow did not induce SWFM. This finding supports our observation that AVP combined with reduced blood flow is a more potent stimulus of SWFM than AVP alone.

One key argument used against LDF as a method is that an average signal of microvascular blood flow does not provide information about the heterogeneity of blood flow in vessels of different diameters (6). Our findings demonstrate that SWFM induced by AVP involves all vessels of the microcirculation including venules (Fig. 4 and Supplemental Video S1). SWFM is suggested to be a spatial network phenomenon, in which, in the vasodilative phase, a minimum number of proximal vessels must intermittently open simultaneously to ensure blood flow from larger vessels (17). In hamster chamber-window preparations, both hemorrhage (19) and intravenous AVP infusion (8) induce the most severe vasoconstriction in smaller-resistance arteries compared with downstream arterioles, thus indicating that the vessel level with the most severe vasoconstriction is of importance in kickstarting SWFM.

An important aspect of standardizing intravital videomicroscopy has been to clarify spatial heterogeneity in microvascular perfusion. An increased spatial heterogeneity index has been correlated with increased mortality in septic patients (27). In our study, the temporal heterogeneity index was increased by more than fourfold compared with the spatial heterogeneity index during AVP infusion (Table 2), confirming that time-wise fluctuations in the microcirculation are of greater heterogeneity than spatial differences. However, time-wise microcirculatory fluctuations have been shown to be coherent within a distance of 5 mm, indicating the occurrence of both time and space fluctuations in the microcirculation (23).

The present guidelines (5) recommend limiting the recording time to 20 s, mainly because of the difficulty in obtaining stable images without pressure artifacts, as well as to minimize data-storage requirements. However, our study suggests that extending recordings beyond 20 s adds important aspects related to temporal fluctuations. A methodological study using both a fixed approach and a surrounding image-acquisition stabilizer has demonstrated that it is possible to extend the length of steady sublingual microcirculatory video recordings in the clinical setting (1). A caveat with the long observation time is that this restricts measurements to one particular area. This may increase the risk for recording in an area that is not representative. The larger standard deviation (Fig. 2) as seen with the fixed setup (1 area) vs. the handheld (mean of 5 areas) may be explained by this.

Study limitations. Immobilization and anesthetics are prerequisites for studying sublingual microcirculation in pigs. Because these drugs reduce the endogenous sympathetic tone, the gross hemodynamics (e.g., systemic pressure and cardiac output) in our animals resemble a sedated patient in the intensive care unit rather than an awake human. Additionally, the juvenile pig differs from humans in having a compensatory high systemic oxygen extraction attributable to a low hemoglobin level (7.6 ± 0.4 g/dl), probably caused by the steep growth curve. We cannot exclude the fact that our findings are affected by these limitations.

Conclusions. Extending the recording time beyond the guideline recommendations revealed a greater reduction in vasopressor-induced microcirculatory impairment. Additionally, with a prolonged observation time, we were able to detect an earlier onset of vasopressor-induced microcirculatory impairment in acute heart failure. These findings indicate that a reevaluation of the present guidelines could improve the assessment of microcirculatory function in critically ill patients.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.
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AUTHOR CONTRIBUTIONS


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