The microcirculatory response during cardiac surgery
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Quantitative imaging of microcirculatory response during nitroglycerin-induced hypotension

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Introduction

More than 20 years ago, Endrich et al investigated the effects of nitroglycerin (NTG)-induced hypotension on microcirculation in a hamster dorsal skin fold model using intravital microscopy, quantitative video image analysis, and a micropuncture system for the determination of microcirculatory pressure. The authors concluded that NTG dilated both arterioles and venules in the microvascular network during hypotension as shown by a decrease in the arteriolar-venular pressure gradient.

NTG is frequently used at low doses in cardiac surgery and intensive care. During cardiac surgery, NTG is often used for the rapid but moderate reduction of the arterial pressure, allowing safe surgical grafting procedures at low ventricular and aortic pressures. Another advantage of NTG in the setting of cardiac surgery is that NTG improves coronary blood flow and has anti-ischemic effects. NTG is also often used during intensive care, at low doses, for recruitment of the microcirculation (eg, in septic patients) or occasionally, at high doses, for rapid reduction of severe hypertension (eg, during hypertensive crises).

Vasodilators causing dilation of the arteries/arterioles can promote microcirculatory flow by distal movement of the pressure front increasing the entrance pressure of the microcirculation thereby promoting microcirculatory flow. Although it is assumed that NTG lowers arterial pressure by mechanisms of venular dilation and promoting microcirculatory recruitment, this has never been confirmed in the human microvasculature under clinical conditions. The authors studied the microcirculatory effects of high-dose NTG induced hypotension in two different patients, with intravital microscopy and reflectance spectrophotometry, both applied sublingually. These two techniques enabled the authors to visualize and quantify the microcirculatory hemodynamics, respectively, and to measure the microcirculatory oxygen availability. The authors chose to investigate the microcirculatory effects of NTG administered in high doses to be able to recognize its direct acute mechanistic effects on microcirculation.

Here, the authors report a similar microcirculatory response to high dose NTG induced hypotension in two clinically different patients.
Quantitative imaging of microcirculatory response during hypotension

Case 1
A 64-year-old male with good ventricular function was admitted for elective off-pump bypass grafting of three coronary vessels. Hemodynamic monitoring was performed via Swan-Ganz and artery radialis catheters. The patient was kept at 37°C. The anesthetic management consisted of infusion of fentanyl and pancuronium and ventilation with a mixture of 50%/50% O₂/N₂O and sevoflurane.

To prevent aortic dissection during aortic-side clamping for proximal graft anastomosis, a bolus of 1.5 mL (50 µg·mL⁻¹) NTG was administered intravenously to reduce systolic blood pressure. After the anastomosis, systemic hypotension was corrected by leg elevation and volume resuscitation. No medication, such as vasopressors, was given to treat hypotension. Simultaneously, microcirculatory changes were visualized using sidestream dark-field (SDF) imaging (MicroScan; MicroVision Medical, Amsterdam, The Netherlands). SDF imaging allows noninvasive handheld video microscopy for direct microscopic observation of microcirculation. The imaging light guide of the hand held microscope is surrounded by light emitting diodes (wavelength = 530 nm). Stroboscopic green light emitted by these diodes is directed at the tissue surface and is absorbed by the hemoglobin of the erythrocytes flowing in the microcirculation. In this way, the flowing erythrocytes in the microcirculation can be clearly observed as flowing dark globules in the microcirculation. In this way, alterations in the morphological properties of the complete network of microvessels, (i.e., arterioles, capillaries, and venules) can be visualized in a surface of 1 mm². The light guide is covered by a sterile plastic cap and was placed on the sublingual tissue surface in such a way as to keep the same network of microvessels in focus during NTG administration without causing pressure artifacts. Sublingual microcirculation was recorded on a digital video recorder and viewed on a monitor with a final magnification of x350. For quantitative evaluation of the images, videos were analyzed off-line using microvascular analysis software (MAS) (MicroVision Medical) to quantify changes in both arteriolar and venular diameter. This software also allows calculation of microvascular blood velocity in a selected segment of microvessels using frame-by-frame image analysis. Consecutive images show the location of erythrocytes as they traverse the microvessels, resulting in space-time diagrams of cell movement (Video 1 [supplementary video is available online]). The slope of each diagram represents the blood velocity.
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Case 2

After successful pulmonary lobectomy, an 85-year-old male was admitted to the intensive care unit. Postoperatively, the patient developed hypertensive crises with episodes of systolic arterial pressure exceeding 250 mmHg. NTG at subsequent doses of 150 µg, 100 µg, and 50 µg was administered intravenously to reduce these extreme blood pressures. SDF imaging was used during the first bolus of NTG, and reflectance spectrophotometry (RS) was used during the subsequent administrations. Microcirculatory RS (O2C; Lea Medizintechnik, Giessen, Germany) consisted of use of an optical fiber placed on the sublingual tissue transmitting light and receiving reflected light from the microcirculatory surface for spectroscopic evaluation. Simultaneous measurement with both techniques was not allowed due to optical interference from both devices. RS measures hemoglobin concentration and hemoglobin oxygen saturation ($\mu$HbSO$_2$) based on spectrum analysis of reflected light by illumination of tissue (500–630 nm). RS also measures the microvascular blood flow (MBF) based on micro-laser Doppler measurements. The measurement depth is approximately one mm, similar to that of the SDF imaging.

Results

Case 1

After NTG, the mean arterial pressure (MAP) decreased rapidly from 90 to 30 mmHg. Leg elevation and volume resuscitation with 250 mL of Ringer’s solution and 250 mL of gelofusine was used to correct the MAP to 65 mmHg after several minutes. In this period, any ST elevation on electrocardiography was not observed.

Figure 1 shows representative images of the sublingual microcirculation before ($T = 0$ min; MAP 90 mmHg), during ($T = 1$ min; MAP 60 mmHg), and after ($T = 3$ min; MAP 30 mmHg) NTG induced hypotension. The images show clearly the microcirculatory volume recruitment in all generations of microcirculatory vessels during the fall in blood pressure followed by an immediate depletion of microcirculatory volume when lowest MAP was reached. These sequences thereby identified in one case, the beneficial (1 min) followed by the unwanted (3 min) microcirculatory effects of the use of high dose vasodilator for the correction of blood pressure during cardiac surgery. Although SDF imaging was also performed after correction of hypotension, the images were from another sublingual location making it impossible to measure changes in diameter and flow in the same microvessel.
Quantitative imaging of microcirculatory response during hypotension

Case 2

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Figure 1. Sublingual microcirculation images during nitroglycerin induced hypotension. An arteriole (A), a capillary (C), and a venule (V) are indicated in the upper images. The lower images are magnifications of the arteriole and the venule.
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An arteriole (A), a capillary (C) and a venule (V) are indicated in these images. Arterioles can be identified as vessels with high velocity and venules with lower velocity. Arterioles branch off to smaller arterioles while the venules come together into a larger venule. The diameter and velocity of the different generation of microvessels seen in the images are shown in Table 1, where three of each type of vessel is shown. As can be observed from the video-images, the sequence of events during NTG-induced hypotension is first, an increase in arteriolar diameter leading to higher blood velocity in these arterioles followed by a subsequent increase in capillary blood velocity, and then, by an increase in venular diameter together with an increased venular blood velocity (T = 1). After this volume shift, the arteriolar diameter and blood velocity collapsed together with an abrupt decrease of capillary blood velocity, venular diameter and venular blood velocity (T = 3).

Case 2

The extreme systolic blood pressure in this patient decreased immediately and dose-dependently upon NTG bolus administrations. After the first bolus of NTG, SDF imaging revealed an improvement of the microcirculatory blood flow. The microvascular blood velocity in venules increased from $253 \pm 84$ to $3104 \pm 623 \mu m/s$ when a bolus of $150 \mu g$ NTG was administered.

Figure 2 shows recordings of sublingual microcirculatory parameters after the subsequent boluses (100 and 50 $\mu g$) of NTG. The MBF (as measured by micro laser Doppler from the RS measurement) also increased, from $162 \pm 35$ to $351 \pm 64$ (arbitrary units), and, as expected, the hemoglobin concentration followed this rise in MBF. The $\mu HbSO_2$ increased after $100 \mu g$ NTG from 79% to 84% but, surprisingly, not after 50 $\mu g$ NTG, possibly indicating that maximum $O_2$ saturation had been attained.

Discussion

Here, the authors demonstrated for the first time the bi-phasic response of the human microcirculatory system to NTG-induced hypotension in a clinical setting. This response to a relatively large dose of NTG is characterized by an initial increase in arteriolar diameter and a reduction in systemic blood pressure, promoting microcirculatory flow. Then, when blood pressure gets too low, this is followed by a phase in which microcirculatory flow can no longer be sustained. This study shows in a single case both the wanted and unwanted effects of the use of NTG in a single maneuver.
Quantitative imaging of microcirculatory response during hypotension

Table 1. Microvascular changes in arteriolar and venular diameter and blood velocity during nitroglycerine induced hypotension. T=0 represents the basal state as reference; T=1 and T=3 represent recordings one and three minutes after NTG administration.

<table>
<thead>
<tr>
<th></th>
<th>T=0 min</th>
<th>T=1 min</th>
<th>T=3 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arteriole 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>7.2</td>
<td>12.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Δ Diameter (%)</td>
<td>Reference</td>
<td>67%</td>
<td>13%</td>
</tr>
<tr>
<td>Velocity (µm/s)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Arteriole 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>5.6</td>
<td>9.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Δ Diameter (%)</td>
<td>Reference</td>
<td>67%</td>
<td>14%</td>
</tr>
<tr>
<td>Velocity (µm/s)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Arteriole 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>5.5</td>
<td>9.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Δ Diameter (%)</td>
<td>Reference</td>
<td>77%</td>
<td>16%</td>
</tr>
<tr>
<td>Velocity (µm/s)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Venule 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>18.5</td>
<td>22.2</td>
<td>18.0</td>
</tr>
<tr>
<td>Δ Diameter (%)</td>
<td>Reference</td>
<td>20%</td>
<td>-3%</td>
</tr>
<tr>
<td>Velocity (µm/s)</td>
<td>424 ± 87</td>
<td>710 ± 82</td>
<td>94 ± 15</td>
</tr>
<tr>
<td><strong>Venule 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>43.7</td>
<td>48.9</td>
<td>42.3</td>
</tr>
<tr>
<td>Δ Diameter (%)</td>
<td>Reference</td>
<td>12%</td>
<td>-3%</td>
</tr>
<tr>
<td>Velocity (µm/s)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Venule 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>18.0</td>
<td>20.9</td>
<td>14.9</td>
</tr>
<tr>
<td>Δ Diameter (%)</td>
<td>Reference</td>
<td>16%</td>
<td>-17%</td>
</tr>
<tr>
<td>Velocity (µm/s)</td>
<td>578 ± 156</td>
<td>1050 ± 254</td>
<td>117 ± 18</td>
</tr>
</tbody>
</table>

NA: not applicable, due to imaging rate limitation of 25 frames/s.
Figure 2. Reflectance spectrophotometry and microlaser-Doppler recordings of sublingual microcirculatory parameters during treatment with nitroglycerin intravenous boluses of 100 and 50 microg. AU, arbitrary units.
Quantitative imaging of microcirculatory response during hypotension

Other studies also investigating the effects of NTG have been conducted by the authors’ group and others. These have generally shown an improvement in microcirculatory flow with the administration of NTG. In this way, the authors showed in a study in pressure guided resuscitation of septic patients that a low dose of NTG was able to improve microcirculatory flow, specifically in the capillaries. In heart failure patients, a low dose of NTG was also used to improve microcirculation. In a recent study using a different vasodilator, ketanserin, the authors showed that, in an adequately volume oased patient, ketanserin was able to reduce blood pressure while maintaining microcirculatory flow.

In the patients, the authors showed the effects of the administration of a vasodilator such as NTG where both microcirculatory recruitment and deterioration of microcirculatory flow were observed. The authors also showed in a double-blind randomized placebo controlled trial that NTG is not always successful in recruiting the microcirculation, and that conformation with a microcirculatory technique may help the clinician to confirm whether NTG therapy has been successful in the expectation of microcirculatory recruitment.

These two cases suggests that the monitoring of sublingual microcirculation by, for example, SDF imaging, may be a useful tool for titrating vasodilators in perioperative use.

REFERENCES
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