Nitроглицерин-индуцированная гетерогенная субэндокардиальная миокардиальная кровь, измеренная кардиоскопией, у пациентов с коронарной артериальной болезнью

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Резюме

Исследовано, увеличивает ли нитроглицерин (НТГ) субэндокардиальную миокардиальную кровь (СМБК), и если это верно, нарушает ли эта кровь артериальный или венозный кровоток у пациентов с коронарной артериальной болезнью. Это исследование было проведено для изучения изменений СМБК под влиянием НТГ.

Изменения в СМБК под влиянием НТГ (200 мкг, внутривенно) были измерены кардиоскопией у 58 сегментов левого желудочка у 58 пациентов с коронарной артериальной болезнью. НТГ-индуцированные красные и фиолетовые эндокардиальные цвета определялись как увеличение артериального и венозного СМБК, соответственно. Эндокардиальный цвет до НТГ был классифицирован как коричневый, светло-коричневый, светлый и белый. Эндоэпикардиальная биопсия обследованного участка и 201Tl сцинтиграфия были проведены в 40 из этих пациентов незамедлительно после кардиоскопии и через несколько дней после кардиоскопии, соответственно.

После НТГ, СМБК увеличилась в 48 из 58 сегментов; артериальная СМБК в 34 и венозная СМБК в 12 сегментах; артериальная СМБК в 24 коричневых и светло-коричневых сегментах; венозная СМБК, артериальная СМБК и без изменения в 12, 10 и 5 сегментах, соответственно; и без изменения в 10 белых сегментах. 201Tl-сцинтиграфия и эндоэпикардиальная биопсия показали, что коричневый, светло-коричневый, светлый и белый эндокардиальные цвета соответствовали нет ишемии, легкой ишемии, тяжелой ишемии и фиброзу, соответственно.

НТГ вызывала увеличение либо артериального или венозного СМБК в зависимости от контрольного эндокардиального цвета, регионального движения стенок сердца и тяжести коронарной стенозы.

Ключевые слова: Нитроглицерин, кардиоскопия, эндокардиальный цвет, субэндокардиальная миокардиальная кровь, артериальный и венозный кровоток

Те субэндокардиальные миокардиальные слои являются уязвимыми для ишемии. Поэтому, улучшение субэндокардиальной миокардиальной кровотока (СМБК) является необходимым условием для лечения коронарной артериальной болезни.

Нитроглицерин (НТГ) является хорошо известным антагонистом артериальных спазмов. Однако, вопрос о том, увеличивает ли НТГ СМБК, и если это так, то в какой степени это влияет на просветление коронарных артерий, до сих пор остается спорным.

СМБК была клинически оценена с помощью сцинтиграфии перфузии,

последующей эмиссионной томографии,

контрарной экхокардиографии,

конконтакного кардиографа,

и других методов,

и увеличение в СМБК было зафиксировано в процессе исследования одним из этих методов.

Коронарные артерии состоят из различных ветвей, которые формируют кокон-образное строение. Поэтому, как артериальный, так и венозный кровоток могут проходить через ишемизированный миокард.

Скардоскопия, вязкая анергетическая артериальная визуализация изнутри, является высокоточным методом кардиоскопии, который позволяет определить направление кровотока в различных участках миокарда.

Методы

Изучено, увеличивает ли нитроглицерин (НТГ) субэндокардиальную миокардиальную кровь (СМБК), и если это верно, нарушает ли эта кровь артериальный или венозный кровоток у пациентов с коронарной артериальной болезнью.

Хотя вопрос о том, увеличивает ли НТГ СМБК, и если это так, то в какой степени это влияет на просветление коронарных артерий, до сих пор остается спорным.

Для данного исследования было проведено кардиоскопическое исследование, чтобы убедиться, что НТГ увеличивает СМБК в левый желудочек, и если это верно, то в какой степени это влияет на просветление коронарных артерий.

Так что, кардиоскопия является эффективным методом для визуализации миокарда изнутри, позволяющим определить направление кровотока и дать представление о состоянии миокарда.

Изучено, увеличивает ли нитроглицерин (НТГ) субэндокардиальную миокардиальную кровь (СМБК), и если это верно, нарушает ли эта кровь артериальный или венозный кровоток у пациентов с коронарной артериальной болезнью.
complicated with stable angina] underwent cardioscopy of the left ventricle after confirmation of coronary stenosis by angiography to examine the effects of intravenous administration of NTG on SMBF. Coronary artery disease was classified according to the criteria described elsewhere.\textsuperscript{10,11} The present study was performed at Toho University Sakura Hospital and Funabashi-Futawa Hospital and was approved by the respective Institutional Review Boards. All the patients provided informed consent for cardioscopy.

**Cardioscopy system:** The cardioscopy system was composed of a light source, 4.5F fibrescope, 9F guiding balloon catheter, intensified chilled coupled device (ICCD) camera, camera controller, DVD recorder, and television monitor.

The fibrescope (AF 14, Olympus Corporation, Tokyo) was composed of a 4.5F fibrescope containing 3000 glass fibers for image guidance and 300 glass fibers for light guidance. The fibrescope could be passed through the 9-F guiding balloon catheter (Clinical Supply Company, Gifu, Japan). The balloon was inflatable with CO\textsubscript{2}. The catheter had a Y connector at the proximal end: one channel for fibrescope insertion and another for saline flush. White balance of the cardioscope was adjusted using white gauze that was immersed in saline solution. The fibrescope and guiding balloon catheter are approved for clinical use by the Japanese Ministry of Health, Labor and Welfare.\textsuperscript{12}

**Evaluation of subendocardial myocardial blood flow (SMBF):** Coronary angiography and left ventriculography were performed first. Diameter stenosis of the coronary arteries was measured using a TCS Symphony 2.02 (McKesson Co). Collateral development was classified by Rentrop.\textsuperscript{13}

After coronary angiography and left ventriculography, a guiding balloon catheter was introduced into the left ventricle and the balloon was inflated with CO\textsubscript{2}. Next, a fibrescope was introduced into the guiding catheter to place the fibrescope tip at the distal most end of the guiding catheter. The balloon was then gently pushed against the endocardial surface of the wall segment (anterior or inferior wall segment), which was irrigated by a coronary artery with significant stenosis. Because the balloon protruded 5 mm ahead of the catheter tip, the distance between the fibrescope tip and the endocardial luminal surface was maintained at approximately 5 mm.\textsuperscript{14} The diameter of the visual field at a distance of 5 mm was approximately 1.2 cm in an in vitro study.\textsuperscript{15} Heparinized saline solution (10 IU/mL) was then infused at a rate of 10 mL/s by a power injector for 5 seconds to displace the blood between the endocardial surface and the fibrescope and to observe the endocardial surface by cardioscopy using a white light. The guiding balloon catheter was preshaped so as to easily locate on the targeted wall segment; “S”- or “crank”-configuration for anterior, apical and inferior wall segments and apex, “J”-configuration for lateral wall segment, and “L”-configuration for high posterior wall segment.\textsuperscript{16}

NTG (200 μg) was injected into the femoral vein, and the changes in endocardial color, which represented SMBF, were observed at 1, 2, 3, and 6 minutes after the injection. The changes in endocardial color were observed in one wall segment in each patient.

Selective intracoronary administration of NTG was not carried out because insertion of an additional catheter was required, and this procedure may have been a further burden to patients.

Cardioscopic images were displayed on a television monitor simultaneously with fluoroscopic images and an electrocardiogram. Details of the cardioscopic procedures are described elsewhere (Figure 1).\textsuperscript{10,12} **Wall motion:** After cardioscopic observation, a contrast material was injected toward the observed wall segment through the channel that was used for the injection of saline solution to observe the regional wall motion. Wall motion was classified as normokinetic-to-hypokinetic when inward motion was observed and akinetic-to-dyskinetic when no motion or outward motion was observed (Figure 1). Quantitative analysis of wall motion was not conducted.

**Classification of endocardial color by cardioscopy:** Endocardial color is brown in patients without heart disease.\textsuperscript{10} In the present study, the control endocardial color of the left ventricular wall in patients was classified into brown, light brown, pale (bluish white closely resembling endocardial color of Langendorff heart in which the blood is replaced by Krebs-Henseleit solution\textsuperscript{10}), and white as has been previously described.\textsuperscript{10} Intraobserver and interobserver agreements on brown, light brown, pale, and white endocardial color before NTG administration were 100%, 83%, 96%, and 90%, respectively, and 100%, 83%, 91%, and 100%, respectively.

**Cardioscope-guided endomyocardial biopsy:** Following cardioscopy, 40 of the 58 patients (7 with brown endocardial color, 7 with light brown endocardial color, 20 with pale endocardial color, and 6 with white endocardial color) underwent endomyocardial biopsy of the wall segment that was observed by cardioscopy.\textsuperscript{10} The remaining 18 patients did not undergo biopsy because of immediate percutaneous coronary intervention or hemodynamic instability.

After observation of the endocardial surface by cardioscopy, the guiding catheter was pulled back a few centimeters, and the fibrescope that was used for observation was replaced by an endomyocardial biopsy system which was developed by the authors of the present study,\textsuperscript{17} and biopsy was performed.
By this procedure, specimens from the observed portions or the adjacent portions of the same wall segment were obtained.

**Determination of arterial and venous blood by cardioscopy:**

Human arterial and venous blood was sampled, mounted on a deck glass, and observed using a cardioscope. Arterial blood was red whereas venous blood was purple. Based on this ex vivo cardioscopy study, it was considered that arterial blood filling occurred when the endocardial surface was red, while venous blood filling occurred when the endocardial surface was purple.

Intraobserver and interobserver agreements on red, purple, or no change of the endocardial surface after NTG administration were 100%, 92% and 92%, and 96%, 96% and 92%, respectively.

**Quantitative assessment of myocardial blood flow by $^{201}$Thallium (Tl)-scintigraphy:**

Quantitative $^{201}$Thallium (Tl)-scintigraphy was performed in 40 patients who underwent endomyocardial biopsy 3 to 7 days after cardioscopy to clarify the relationships among severity of myocardial ischemia, endocardial color and histological changes. The maximum intensity of $^{201}$TI-scintigraphy was defined as 100% of blood flow, and blood flow in each wall segment was expressed as a percentage of the maximum intensity. The relationships between blood flow and endocardial color were examined.

**Histology:**

The specimens obtained were fixed with 10% formaldehyde solution, cut into successive 10 μm thick slices, and stained by Azan staining. The number of mononuclear cells per microscopic field at × 400 was counted. Cardiomyocyte degeneration, disruption, loss and irregularity were examined. Interstitial edema was defined as a translucent space between the cardiomyocytes with a diameter exceeding the diameter of the neighbouring cardiomyocytes. Fibrotic area was measured by microphotometry using the slices stained by Masson trichrome staining, and a fibrotic area 5% ≤ of microscopic field at × 400 was considered to be fibrosis.

**Statistical analysis:**

The data obtained are expressed as the mean ± standard deviation (SD). The data were tested either by Student’s $t$ test or Fisher’s exact test. A $P < 0.05$ was considered significant.

**RESULTS**

**Cardioscopic changes in endocardial color induced by NTG:**

Figure 2 shows cardioscopic images of the normokinetic-to-hypokinetic anterior wall of the left ventricle in a patient with old myocardial infarction (3 vessel disease; 3 months after ST-elevation myocardial infarction) complicated with stable angina. The endocardial color was pale before NTG. The color changed to red 2 minutes after administration of NTG, indicating an increase in arterial SMBF.

Figure 3 shows cardioscopic images of the akinetic-to-dyskinetic inferior wall in a patient with an old myocardial infarction (3-vessel disease; 2 months after ST-elevation myocardial infarction) complicated with stable angina. This wall segment was originally pale and then changed to purple, indicating an increase in venous SMBF.

**Changes in systemic blood pressure and heart rate induced by NTG:**

Following NTG administration, peak systolic left ventricular pressure decreased from 134 ± 24 to 124 ± 20 mmHg ($P < 0.001$), end-diastolic left ventricular pressure decreased from 23 ± 5 to 20 ± 5 mmHg ($P < 0.0001$), and heart rate increased from 68 ± 7 to 71 ± 10 beats/minute ($P < 0.0001$).

**Time course changes in SMBF induced by NTG:**

No obvious changes were observed in endocardial color one minute after injection of NTG in the majority of wall segments, indicating no increase in AMBF. At 2 minutes, the color changed to red in 28 wall segments, which indicates arterial blood flow, and to
Table I. Relationship Between Changes in Subendocardial Myocardial Blood Flow (SMBF) Assessed by Cardioscopy and the Time-lag From Nitroglycerin (NTG) Injection

<table>
<thead>
<tr>
<th>Time from NTG injection (minutes)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial SMBF (%)</td>
<td>7</td>
<td>28*</td>
<td>34†</td>
<td>34‡</td>
</tr>
<tr>
<td>Venous SMBF (%)</td>
<td>(12)</td>
<td>(48)</td>
<td>(59)</td>
<td>(59)</td>
</tr>
<tr>
<td>Arterial and Venous SMBF (%)</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>No change (%)</td>
<td>(0)</td>
<td>(10)</td>
<td>(21)</td>
<td>(21)</td>
</tr>
</tbody>
</table>

* P < 0.05, † P < 0.01 versus 1 minute.

Table II. Relationship Between Control Endocardial Color and Nitroglycerin-induced Changes in Subendocardial Myocardial Blood Flow (SMBF)

<table>
<thead>
<tr>
<th>Control endocardial color</th>
<th>Brown</th>
<th>Light brown</th>
<th>Pale</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>7</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Arterial SMBF (%)</td>
<td>17††</td>
<td>7††</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Venous SMBF (%)</td>
<td>(100)</td>
<td>(100)</td>
<td>(38)</td>
<td>(0)</td>
</tr>
<tr>
<td>No change (%)</td>
<td>(0)</td>
<td>(0)</td>
<td>(44)</td>
<td>(0)</td>
</tr>
</tbody>
</table>

n = number of wall segments. * P < 0.05, † P < 0.01 versus pale. †† P < 0.05, ††† P < 0.01 versus white. ‡ P < 0.05 versus brown and light brown.

Table III. Relationship Between Left Ventricular Wall Motion and Nitroglycerin-induced Changes in Subendocardial Myocardial Blood Flow (SMBF)

<table>
<thead>
<tr>
<th>Wall motion</th>
<th>Normokinetic to hypokinetic</th>
<th>Akinetic to dyskinetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Arterial SMBF (%)</td>
<td>(32)</td>
<td>2†</td>
</tr>
<tr>
<td>Venous SMBF (%)</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>No change (%)</td>
<td>(18)</td>
<td>8†</td>
</tr>
</tbody>
</table>

† P < 0.05, †† P < 0.01 versus normokinetic to hypokinetic.

Changes in endocardial color before and after NTG administration: Endocardial color was brown, light brown, pale, or white before NTG administration. Upon administration of NTG, endocardial color changed to the following patterns: red in all 17 brown and 7 light brown segments, indicating increased arterio-venous SMBF in 59% and venous SMBF in 21% (Table I).

Figure 4. Relationships among cardioscopic images, 201Tl-scintigraphic images and histological changes. From A to D: Brown anterior segment of the left ventricle in a patient with stable angina with nonstenotic left anterior descending artery (LAD), light brown anterior wall segment in a patient with stable angina due to 75% stenosis of LAD, pale anterior segment in a patient with stable angina due to 99% stenosis of LAD, and white anterior segment in a patient with old myocardial infarction due to 100% stenosis of LAD. From A-1 to D-1: corresponding rest 201Tl-scintigraphic images: no anterior wall ischemia, mild anterior wall ischemia, severe anterior wall ischemia, and severe anterior wall ischemia, respectively. Anterior wall segments are indicated by arrows in A to D. Histological changes of the corresponding anterior wall segments: no obvious changes in A-2 and B-2, interstitial edema in C-2, and fibrosis (arrow) and cardiomyocyte loss in D-2. Bars in A-2 to D-2 = 100 μm.
Table VI. Relationships Among Endocardial Color, Severity of Myocardial Ischemia Assessed by \(^{201}\)Thallium –scintigraphy, and Histological Changes

<table>
<thead>
<tr>
<th>Endocardial color</th>
<th>Yellow</th>
<th>Light brown</th>
<th>Pale</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Brown</td>
<td>Light brown</td>
<td>Pale</td>
<td>White</td>
</tr>
<tr>
<td>A. (^{201})Tl-scintigraphy</td>
<td>84±7</td>
<td>64±6</td>
<td>41±5</td>
<td>28±12</td>
</tr>
<tr>
<td>Stress (%)</td>
<td>78±7</td>
<td>72±6</td>
<td>63±5</td>
<td>30±12</td>
</tr>
<tr>
<td>Rest (%)</td>
<td>78±7</td>
<td>72±6</td>
<td>63±5</td>
<td>30±12</td>
</tr>
<tr>
<td>B. Histology</td>
<td>1) Cardiomyocytes</td>
<td>Degeneration</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irregularity</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disruption</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2) Mononuclear cell infiltration</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3) Interstitial edema</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4) Fibrosis</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Endocardial</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

\(n = \) number of wall segments. \(P < 0.05, \quad \) \(P < 0.01 \) versus brown. Myocardial blood flow assessed by \(^{201}\)Tl-scintigraphy was not decreased in brown wall segments, slightly decreased in light brown wall segments, and severely decreased in pale and white wall segments. Cardiomyocyte loss and fibrosis were observed in white wall segments, indicating an old myocardial infarction.

Discussion

The following factors are considered to influence blood flow in the subendocardial microvessels: 1) autoregulation of the microvesseis; 2) direct compression by the surrounding myocardium; 3) left ventricular luminal pressure; 4) blood pressure in the irrigating large arteries; 5) blood pressure gradient between the microvessels located in the normal wall and those located in the diseased wall; 6) interstitial pressure surrounding the microvessels, which is generated by contraction of the surrounding myocardium; 7) interstitial pressure gradient across the wall and between the normokinetic and diseased walls; 8) tension-time index/diastolic pressure-time index; 9) pressure gradient between the microvessels and the venous trees, and 10) regional difference in microvessel density, which may be altered by angiogenesis. All of these are directly or indirectly influenced by NTG.

In the present study, NTG-induced changes in SMBF were dependent on control endocardial color, which was demonstrated by \(^{201}\)Tl-scintigraphy and histology to represent severity of myocardial ischemia and fibrosis, regional wall motion, and severity of stenosis of the irrigating artery.

An increase in arterial SMBF was observed more frequently in the wall segments with brown and light brown endocardial color, with preserved contraction, and irrigated by an artery less than 99% in stenosis. It is conceivable that arterial SMBF increased because the myocardium was intact and the vascular bed was preserved and the irrigating artery was not totally occluded; therefore, arterial blood supply from the irrigating artery overcame other factors, such as shortened diastolic phase due to increased heart rate and decreased perfusion pressure of the irrigating artery due to a decrease in systemic blood pressure, which might have acted to decrease arterial blood supply.

It is known that backflow from the venous trees into the ischemic myocardium can occur. It is conceivable that NTG enhanced the blood backflow from the venous trees into the pale subendocardial myocardium because arterial blood supply was sparse, causing purple endocardial coloration.

Comparison of cardioscopy and other imaging modalities: The imaging modalities that currently clinically assess SMBF may not discriminate between arterial and venous blood flow. If venous blood flow is imaged and evaluated as blood flow recovery, it is misinterpreted as effective arterial blood flow recovery. However, it is not effective blood flow recovery but luxury blood flow recovery because venous blood is only slightly utilized by the ischemic myocardium.
In contrast with other imaging modalities, arterial and venous SMBF were discriminated in the present study by using cardioscopy. Although subjective, cardioscopy can be potentially used for the determination of arterial or venous SMBF.

Although invasive, cardioscopy is feasible for clinicians who are skillful at cardiac catheterization. Replacing a catheter that is used for left ventriculography by a cardioscope is easy and the time required for cardioscopic examination of the effects of NTG is around 10 minutes.

Oxygen saturation, oxy-haemoglobin and deoxy-haemoglobin in the subendocardial myocardium can be measured through the cardioscope by employing a near-infrared light to quantitatively assess myocardial oxygen dynamics. Cardioscopy may therefore contribute to obtaining direct evidence as to whether or not a given drug, including NTG, results in a recovery of myocardial ischemia and may give an objective basis for selection of other drugs in individual patients with coronary artery disease.

Study limitations: 1) Although arterial and venous SMBF were determined by cardioscopy, observation of blood flow in the myocardium deeper than the subendocardial myocardium is beyond the scope of cardioscopy. 2) Cardioscopic observation of multiple wall segments was not conducted because the amount of saline solution required for blood displacement was limited to 500 mL in order to avoid occurrence of acute congestive heart failure.

Conclusions: NTG caused either an increase in arterial or venous SMBF depending on endocardial color, which represented the severity of myocardial ischemia and fibrosis. An NTG-induced increase in venous SMBF has not ever been demonstrated clinically.

REFERENCES

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