◎原 著

Non-invasive study for peripheral circulation in patients with diabetes mellitus

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Abstract : The purpose of this study is to establish a new, non-invasive diagnostic technique for peripheral circulation in patients with diabetes mellitus in the early stage of arteriosclerosis obliterans (ASO) as one of the complications of diabetes mellitus. We observed peripheral circulation quantitatively by thermography and Laser-Doppler blood flowmetry. The body surface peripheral circulation in 27 patients with diabetes mellitus, including 14 males and 13 females with a mean age of 67.4 years (range from 51-82 years), and with a mean hemoglobin A1C (HbA1C) of 9.5% (range from 6.8%-13.0%), and who were suffering coldness, numbness or pain in their feet, was examined using thermography and Laser-Doppler blood flowmetry. Thermographic results were analyzed quantitatively by calculating a recovery ratio as : Recovery ratio= [Total counts of thermography (Pixels) over temperature (T) after cold-loading] ÷ [Initial counts over T after hot-loading] ×100 (%).

Results of recovery ratios for 27 cases were 0%-93.5%, and the average was 34.0%. At the same time, the blood flow after cold-loading was 0.91-5.36ml/min/100g tissue and the average was 2.04ml/min/100g tissue. We found that the recovery ratio and the blood flow were correlated ($r=0.634$, $p<0.0001$). The recovery ratio for males was 28.4% and that of females was 39.9%, and there was a tendency for the recovery ratio of females to be higher than males, however, this was not statistically significant. There was a correlation between the recovery ratio and age ($r=0.187$, $p<0.0001$), although, the correlation was low. There was also a slight correlation between the recovery ratio and HbA1C ($r=0.041$, $p<0.001$). On the other hand, the blood flow of males was 2.03ml/min/100g tissue and that of females was 2.05. There was a tendency for the recovery ratio of females to be higher than males, however, the correlation was not significant. There was a correlation between blood

flow and age ($r=0.110$, $p<0.0001$), however, the correlation was low. There was also a slight negative correlation between blood flow and HbA1C ($r=-0.179$, $p<0.0001$).

The ratio of the blood flow after cold-loading at 20℃ divided by the blood flow after hot-loading at 36℃ was 38.1%-122%, and the average was 80.6%. There was correlation between this ratio and the recovery ratio ($r=0.502$, $p<0.0001$). The case of the peripheral blood flow recovered immediately to the amount of the hot-loading or access amount of hot-loading after cold-loading, and had a high recovery ratio of thermography. This might mean that the cooled body surface was warmed by over-circulation of blood flow to keep body temperature at 36℃ in the mean of homeostasis.

We showed that thermography and Laser-Doppler blood flowmetry were useful for non-invasive study to separate patients with poor peripheral circulation. We recommend that these methods for evaluation of further treatment, such as with Prostaglandin E1, on peripheral circulation in patients with diabetes mellitus and ASO.

Key word : diabetes mellitus, peripheral circulation, thermography, Laser-Doppler blood flowmetry, blood flow

Introduction

The number of patients with diabetes mellitus is increasing rapidly, as human lifestyles and eating habits are changing. Patients with diabetes mellitus have many complications, such as retinopathy, nephropathy, neuropathy, and deep ulcerat-ions and gangrene of the lower extremities[1,2]. We have observed body surface temperature by thermography for the purpose of estimating peripheral blood flow. Thermography[3] is a useful method for body imaging, along with other systems like computed tomography (CT) and magnetic resonance imaging (MRI). In a previous paper[4], we quantified the results of thermography so that it can be useful for studies on body surface temperature in patients with diabetes mellitus. We also introduced a new pre-loading technique with hot water at 36℃ for 5 min (hot-loading) for thermography to reduce the influence of weather so reliable observations could be made during different seasons[5].

Here, in a continuation of our previous studies, we observed peripheral circulation quantitatively by thermography[4,5] and Laser-Doppler blood flowmetry[6], in order to prevent deep ulcerations and gangrene of the lower extremities at on early stage. We first discuss the results of thermography in combination with another quantitative method for blood flow, Laser-Doppler blood flowmetry[6]. Secondly, we observe the blood flow in lower limbs under different conditions : 1) submerged and warmed for 5 min in a hot bath at 36℃ (i. e. hot-loading)[5], and 2) submerged and cooled for 5 min in a water bath at 20℃ (i. e. cold-loading)[4] in order to observe the response against cold-loading and to find the optimum conditions for Laser-Doppler blood flowmetry and thermography.

Finally, we show that the difference of blood flow between post hot-loading and post cold-loading in patients with diabetes mellitus was important for coldness in their feet.

Subjects and Methods

The body surface peripheral circulation in 27 patients with diabetes mellitus who were suffering coldness, numbness, or pain in their feet, was examined using a high sensitivity infrared ray thermotracer 6T66 (NEC-Sanei Co. Japan) and a Laser-Doppler blood flowmetry ALF21D (Advance Co. Japan)[6]. The patients included 14 males and 13 females, with a mean age of 67.4 years (range from 51-82 years), and with a mean HbA1C of 9.5% (range from 6.8 %-13.0%). The subjects were placed for 15min in a room controlled at a temperature of 20℃ and with relative humidity (60%-70%), as described in our previous paper[4]. Both lower limbs were submerged and cooled for 5min in a water bath containing 10 ℓ of water cooled at 36℃ (i. e. hot-loading) to reduce the effect of weather[5]. Water was wiped off from both lower limbs, and the upper side of bilateral lower limbs, 10cm from Malleolus lateralis, was covered with aluminum foil and cotton towels to limit the area of observation, and to reduce infrared radiation in the background. Thermographs were taken 10min after hot-loading in order to observe the initial area that was not influenced by outside weather, especially during the winter season. The body surface area at temperatures higher than the chosen baseline temperature of 27℃ was calculated with computer software for picture processing (Temperature data transport and processing program Type 9610M for the thermotracer, NEC-Sanei Co. Japan), and was used as an initial area (Pixels) for observation. At the same time, five points for each foot, were observed by Laser-Doppler blood flowmetry. Detectors (ALC probe type C, Advance Co. Japan) were placed using double-stick tape on the base of each toe ; placed on the inside of the base of the toe to avoid bones. The duration of the observation was 3 min for each point, and the lowest stable reading was used. The average blood flow obtained from 10 points was used for further analysis.

Next, the covers were stripped off, and both lower limbs were submerged and cooled for 5min in a water bath containing 10 ℓ of water cooled at 20℃ (i. e. cold-loading)[4]. Water was wiped off from both lower limbs, and both limbs were re-wrapped with aluminum foil and cotton towels. Another set of thermographs was taken 30min after cold-loading for calculation of the recovery ratio. The data obtained were processed using the computer software mentioned above. Recovery ratio was calculated as : Recovery ratio= [Total counts of thermography (Pixels) over temperature (T) after cold-loading] ÷ [Initial counts over T after hot-loading] × 100 (%). A baseline temperature of 27℃ was used for picture processing in this study. Following the second thermography and the second measurement of blood flow by Laser-Doppler blood flowmetry were done after this cold-loading, as described in above.

The ratio of the blood flow after cold- loading at 20℃ divided by the blood flow after hot-loading at 36℃ was calculated individually, and shown as a percentage for further analysis.

Results

Results of recovery ratios for 27 cases were 0%-93.5%, and the average was 34.0%. At the same time, the blood flow after cold-loading was 0.91-5.36ml/min/100g tissue and the average was 2.04ml/min/100g tissue. We found that the recovery ratio and the blood flow were correlated ($r=0.634$, $p<0.0001$, Fig.1).

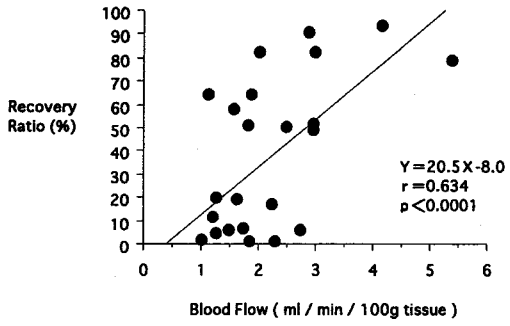

Fig. 1. The recovery ratio (%) of thermography and peripheral blood flow after cold-loading in patients with diabetes mellitus.

The blood flow after hot-loading was 0.91-6.24ml/min/100g tissue and the average was 2.53ml/min/100g tissue. The recovery ratio and the blood flow after hot-loading were correlated ($r=0.483$, $p=0.0002$). The relation between the recovery ratio and blood flow after cold-loading was higher than that after hot-loading.

The recovery ratio for males was 28.4% and that of females was 39.9%. There was a tendency for the recovery ratio of females to be higher than for males, however, there was no statistically significant correlation (Fig. 2).

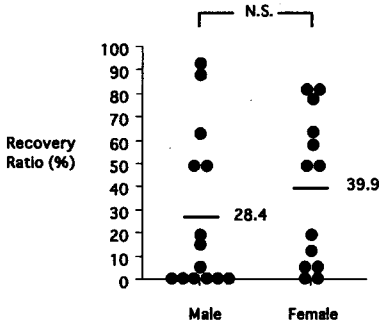

Fig. 2. The recovery ratio (%) of thermography after cold-loading in male and female patients with diabetes mellitus.

The average age of males was 64.1 years (range from 51-82 years), and the average age of females was 71.1 years (range from 64-81 years) ; males were younger than females ($p<0.05$) (data not shown). The average HbA1C of males was 9.3% (range from 7.3-12.5%), and the average HbA1C of females was 9.6% years (range from 6.8-12.6%). There was no significant difference between the average of HbA1C of males and female (data not shown).

There was a low correlation between the recovery ratio and age ($r=0.187$, $p<0.0001$, Fig. 3). Also, there was a slight correlation between the recovery ratio and HbA1C ($r=0.041$, $p<0.001$, Fig. 4).

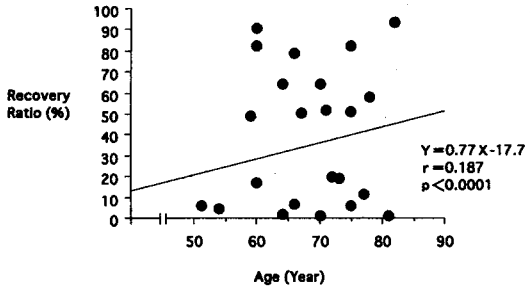

Fig. 3. The recovery ratio (%) of thermography after cold-loading and age in patients with diabetes mellitus.

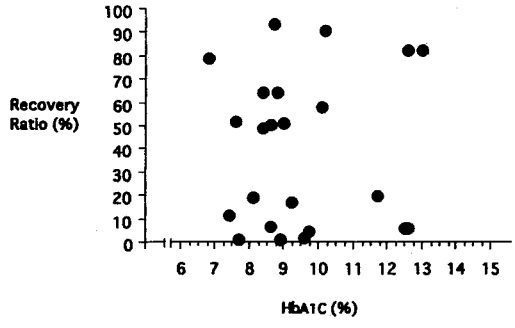

Fig. 4. The recovery ratio (%) of thermography after cold-loading and hemoglobin A1C in patients with diabetes mellitus.

On the other hand, the blood flow of males was 2.03ml/min/100g tissue and that of females was 2.05. There was a slight tendency for the blood flow of females to be higher than males (Fig. 5). There was a low correlation between the blood flow and age ($r=0.110$, $p<0.0001$, Fig. 6). Further, there was a low negative correlation between blood flow and HbA1C

(r=-0.179, p<0.0001, Fig. 7). There was a low negative correlation between age and HbA1C (r=-0.259, p<0.0001, data not shown).

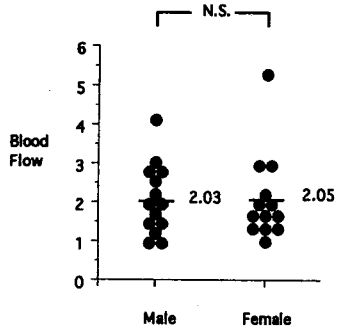

Fig. 5. Blood flow after cold-loading in male and female patients with diabetes mellitus.

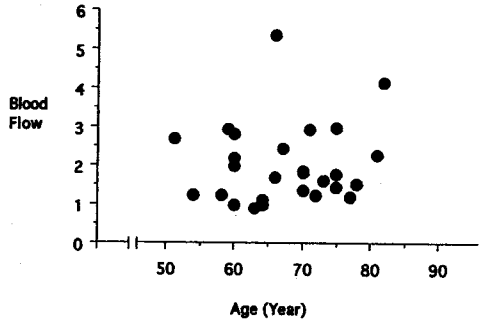

Fig. 6. Blood flow after cold-loading and age in patients with diabetes mellitus.

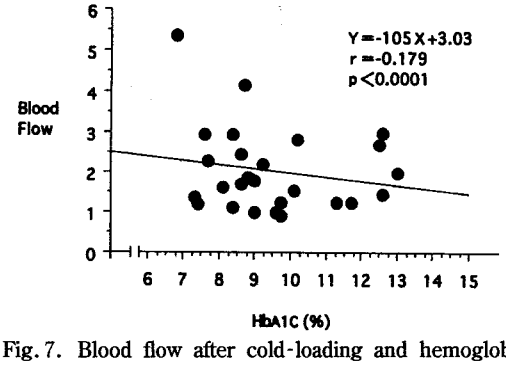

Fig. 7. Blood flow after cold-loading and hemoglobin A1C in patients with diabetes mellitus.

The ratio of the blood flow after cold- loading at 20℃ divided by the blood flow after hot-loading at 36℃ was 38.1%-122%, and the average was 80.6%. There was a correlation between this ratio and the recovery ratio (r=0.502, p<0.0001, Fig. 8).

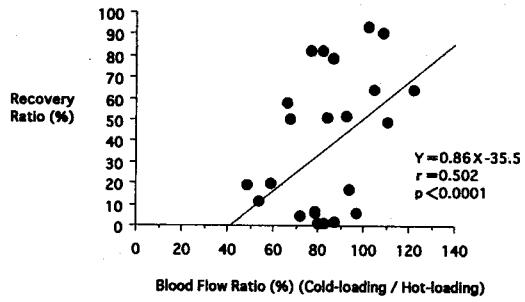

Fig. 8. The recovery ratio (%) of thermography and the ratio of peripheral blood flow (cold-loading/hot-loading) in patients with diabetes mellitus.

Discussion

We have quantified the results of thermography for the study of peripheral circulation, and found that there was good correlation between the result of thermography and that of Laser-Doppler blood flowmetry in the peripheral circulation in patients with diabetes mellitus. Hitoi and Matsuoka (1990) mentioned the usefulness of thermography for analysis of peripheral circulation[7]. We show the results of a study with 27 patients with diabetes mellitus (Fig. 1), and We find that the recovery ratio and blood flow are correlated (r=0.634, p<0.0001). This result might indicate that low temperature in the lower extremities and low peripheral circulation are good indicators for such complications with diabetes mellitus as arteriosclerosis obliterans (ASO).

Next, we examined the correlation between the recovery ratio and sex, age, and HbA1C (Fig. 2, 3, 4). We also examined the correlation between blood flow and sex, age, and HbA1C (Fig. 5, 6, 7). No correlation was higher than between the recovery ratio and blood flow.

In the study about age, there was tendency for older patients to have higher recovery ratio and higher blood flow, however, there was

little statistical correlation. In the background of these patients, older patients had low HbA1C, which we selected the highest number in their past clinical records individually.

There is a possibility that we examined mild diabetes mellitus in older patients and severe diabetes mellitus in younger patients. It might be difficult to be alive longer than the average life length, however, for patients with severe diabetes mellitus in their onset or controlled insufficiently.

Finally we tried to compare conditions such as cold-loading and hot-loading for further studies. We found a higher correlation between thermography and the result of Laser-Doppler blood flowmetry after cold-loading, compared to Laser-Doppler blood flowmetry after hot-loading. The condition of cold-loading reflected the patient's low peripheral circulation.

Finally, we found that the difference in the blood flow between post cold-loading and post hot-loading had a relationship with the recovery ratio. To show this, the difference ratio of blood flow was introduced (Fig. 8). There was a correlation between the recovery ratio of thermography and the ratio of blood flow ($r=0.502$, $p<0.0001$). This means that patients with good recovery after cold-loading in their blood flow within 30 min had good recovery in their skin surface temperature. Some of them (5 out of 27) had difference ratios of more than 100% and had good recovery ratio at more than 50% in thermography. This might mean that the cooled body surface was warmed by over-circulation of blood flow to keep the body temperature at 36℃ in the mean of homeostasis. However, other patients' mechanism might be damaged by diabetes mellitus.

From these observations, we concluded that there was a correlation between the result of thermography and Laser-Doppler blood flowmetry in peripheral circulation of patients with diabetes mellitus. We showed that thermography and Laser-Doppler blood flowmetry were useful as a non-invasive technique to reveal patients with poor peripheral circulation. We recommend these methods for the diagnosis at the early stage of ASO in patients with diabetes mellitus and for evaluation of further treatment such as Prostaglandin E_1 on peripheral circulation in patients with diabetes mellitus and ASO.

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糖尿病患者における末梢循環の非侵襲的検査

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糖尿病患者における閉塞性動脈硬化症の合併を早期に診断，予知，予防する目的で末梢循環障害の程度を非侵襲的にかつ客観的に測定することを試みた。非侵襲的測定方法としてサーモグラフィーとレーザードップラー血流計を同時に用い，得られた結果を数量化した。症例は，下肢に冷え症，しびれ感，下肢痛を有した51歳から82歳までの27症例（平均年齢67.4歳）であった。性別は，男性14例，女性13例，HbA1Cは6.8%～13.0%，平均9.5%であった。サーモグラフィーで得られた結果は回復率として数量化して表示された。回復率の算出方法は回復率＝[20℃冷水負荷後の27℃以上の体表面温度のサーモグラフィーの画素（Pixel）の総数]÷[36℃の温水負荷後の27℃以上の体表面温度のサーモグラフィーのPixelの総数]×100%で求めた。

サーモグラフィーにより測定された回復率は0%～93.5%の範囲にあった。平均は34.0%であった。レーザードップラー血流計により20℃冷水負荷後に測定された血流量は0.91～5.36ml／min／100g tissue の範囲にあった。平均は2.04ml／min／100g tissueであった。得られたサーモグラフィーの回復率とレーザードップラー血流計の血流量との間には正の相関関係を認めた（$p<0.0001$，$r=0.634$）。36℃の温水負荷後に測定された血流量とサーモグラフィーの回復率との間には20℃冷水負荷後同様に相関関係（$p=0.0002$，$r=0.483$）を認めたが，相関係数は20℃冷水負荷後に比較して低値であった。

性別と回復率との間には男性28%，女性40%で女性の方が回復率が高い傾向にあったが，2群間に有意差を認めなっかた。年齢と回復率の間には正の相関関係（$p<0.0001$，$r=0.187$）を認めたが相関係数は低値であった。HbA1Cと回復率との間には正の相関関係（$p<0.001$，$r=0.041$）を認めたが相関係数は低値であった。

一方，性別と血流量との間には男性2.03，女性2.05ml／min／100g tissueで女性の方が血流量が多い傾向にあったが，2群間に有意差を認めなっかた。年齢と血流量との間には正の相関関係（$p<0.0001$，$r=0.110$）を認めたが相関係数は低値であった。HbA1Cと血流量との間には負の相関関係（$p<0.0001$，$r=-0.179$）を認めたが相関係数は低値であった。36℃温水負荷時の血流量を100%とした時の20℃冷水負荷時の血流量の割合を求めたところ38.1%～122%の範囲にあった。平均は80.6%であった。冷水負荷後の血流量の温水負荷時との比と回復率との間には正の相関関係を認めた（$p<0.0001$，$r=0.502$）。このことは，末梢血流量が冷水負荷後，速やかに冷水負荷前値に回復するか，あるいはさらに前値よりも上回って増加する症例においては末梢皮膚温度の回復率が高いことが示された。

糖尿病患者における末梢循環障害の程度をサーモグラフィーとレーザードップラー血流計を同時に用い非侵襲的にかつ客観的に測定することが可能であった。今後，両者の併用は糖尿病患者における閉塞性動脈硬化症の合併の早期診断，予知，予防に役立つことのみならず，末梢循環障害の程度に応じた治療とその効果について定量的な評価に有用な方法と考えられた。

索引用語：糖尿病，末梢循環，サーモグラフィー，レーザードプラー血流計，血流量