Altered Myocardial Vasodilatation in Patients With Hypertriglyceridemia in Anatomically Normal Coronary Arteries

Ikuo Yokoyama, Tohru Ohtake, Shin-ichi Momomura, Katsunori Yonekura, Naoshi Kobayakawa, Teruhiko Aoyagi, Seiryo Sugiiura, Yasuhiro Sasaki, Masao Omata

Abstract—Reduced myocardial vasodilatation (MVD) in hypercholesterolemics without overt coronary stenosis has been reported. However, the status of MVD in hypertriglyceridemias has not yet been clarified. The aim of this study was to investigate whether MVD is impaired in patients with hypertriglyceridemia without overt coronary stenosis. Twenty-three hypertriglyceridemia patients (10 normocholesterolemic hypertriglyceridemia [HTGs] and 13 mixed combined hyperlipidemias [MCHLs]) and 13 age-matched controls were studied. All patients were proven to have more than one normal coronary artery, as diagnosed by coronary angiography, and those segments that were perfused by anatomically normal coronary arteries were used in the study. Myocardial blood flow (MBF) during dipyridamole (DP) loading and baseline MBF were measured by using positron emission tomography and $[^12]N$ ammonia, after which MVD was calculated. Baseline MBF (mL · min$^{-1}$ · 100 g$^{-1}$) was comparable among HTG (76.0±26.1), MCHL (77.0±26.1), and controls (80.3±38.5). However, MBF during DP loading was significantly lower in MCHL (159±52.5) than in control subjects (292±166, P<.01), while it was comparable in HTG (202±104) and controls (3.73±1.14). MVD was significantly reduced in both HTG (2.70±1.09, P<.05) and MCHL (2.07±.70, P<.01) compared with controls (3.08±1.06). However, the status of MVD in hypertriglyceridemias has not yet been clarified. The aim of this study was to investigate whether reduced MVD is a factor in coronary stenosis. Reduced MVD has been thought to be a factor in coronary stenosis. It has been shown that MVD can be altered without evidence of ischemia in hypercholesterolemics and that there is a significant inverse relationship between MVD and plasma triglycerides. In fact, alterations in MVD without overt coronary stenosis have been indicated in a variety of conditions; for example, hypertrophic cardiomyopathy, dilated cardiomyopathy, and diabetes with and without associated hypertension, and in normal segments in patients with myocardial infarction. We have reported a reduced MVD without overt coronary stenosis in patients with hypercholesterolema. However, most recent studies, including our own, involved patients with pure hypercholesterolema or mixed combined hyperlipidemia. The specific role of hypertriglyceridemia in MVD in angiographically normal coronary arteries remains uncertain.

The first aim of this study was to clarify whether MVD in hypertriglyceridemias is reduced in segments perfused by angiographically normal coronary arteries and the second was to compare MVD between HTG and MCHL subjects.

Methods

Study Population

Twenty-three hypertriglyceridemia patients (18 males, 5 females) and 13 normolipidemic, normoglycemic asymptomatic control subjects without a history of heart disease or chronic disease (8 males, 5 females) were involved in this study. Two female patients (1 MCHL, 1 HTG) and 1 female control subject were premenopausal. Of the 23 hypertriglyceridemias, 10 were HTG, as defined by a total TG level >200 mg/dL and TC <220 mg/dL with a longer than 14-hour fast, and 13 were MCHL, as defined by a total TG level >200 mg/dL and TC >220 mg/dL under the same fasting condition. No subject had received lipid-lowering agents before the study. All of the hypertriglyceridemias had atypical chest pain, typical angina, or old myocardial infarction occurring more than 6 months before the PET and had undergone CAG, which confirmed one or two normal coronary arteries within the three major branches, as diagnosed by three independent specialists (zero percent stenosis). Details of CAG findings are shown in Table 1. General characteristics of our study subjects

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294
are summarized in Table 2. There were no significant differences among the three groups in the parameters that include sex, body weight, height, body mass index, blood pressure, smoking, and HbA1c level; there was a significant difference in age, however. All subjects were informed of the nature of the study, after which they agreed to participate in the protocol, which was approved by the local ethics committee.

PET
Regional MBF (mL·min⁻¹·100 g⁻¹) at rest and during DP loading was measured using PET and [¹³N]ammonia. Myocardial flow images were obtained using a Headtome IV PET scanner (Shimadzu Corp). This PET scanner has seven imaging planes; in-plane resolution is 4.5 mm at full width at half maximum and the z-axial resolution is 9.5 mm at full width at half maximum. Effective in-plane resolution was 7 mm after using a smoothing filter. The sensitivity of the Headtome IV scanners is 14 and 24 kcps (μCi/mL) for direct and cross planes, respectively.

After acquiring transmission data over 8 minutes to correct for photon attenuation before obtaining the PET emission images, 15 to 20 mCi of [¹³N]ammonia was injected, and dynamic PET scanning was performed for 2 minutes and static PET scanning for 8 minutes. The dynamic PET scan was performed every 15 seconds (eight times) during the 2-minute period. Dynamic data were obtained for seven slices. Only one channel ECG monitoring in limb leads was made during the PET study. ECG monitoring was performed but was not satisfactory because the precordial ECG record could not be monitored due to technical difficulty; therefore, there was the possibility that ECG data would be unreliable.

TABLE 1. CAG Findings in Study Subjects

<table>
<thead>
<tr>
<th>CAG Findings</th>
<th>Control</th>
<th>HTG</th>
<th>MCHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero vessel disease</td>
<td>...</td>
<td>3</td>
<td>9 (5 after PTCA)</td>
</tr>
<tr>
<td>One vessel disease</td>
<td>...</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>LAD</td>
<td>...</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>LCX</td>
<td>...</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RCA</td>
<td>...</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Two vessel disease</td>
<td>...</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>LAD+LCX</td>
<td>...</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>LAD+RCA</td>
<td>...</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LCX+RCA</td>
<td>...</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

| Number of patients with old myocardial infarction | ... | 1 | 2 |

LAD indicates left descending coronary artery; LCX, left circumflex coronary artery; and RCA, right coronary artery; and PTCA, percutaneous transluminal coronary angioplasty.

TABLE 2. General Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MCHL</th>
<th>HTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (M/F)</td>
<td>13 (8/5)</td>
<td>13 (9/4)</td>
<td>10 (9/1)</td>
</tr>
<tr>
<td>Age, y</td>
<td>56.4±8.1</td>
<td>56.7±7.3</td>
<td>55.3±10.7</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>63.3±5.9</td>
<td>68.2±13.8</td>
<td>64.1±8.5</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.64±6.9</td>
<td>1.64±12</td>
<td>1.60±0.79</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.7±2.0</td>
<td>23.3±2.5</td>
<td>25.3±2.3</td>
</tr>
<tr>
<td>SBP (R), mm Hg</td>
<td>126±10.4</td>
<td>140±31.5</td>
<td>142±16.2</td>
</tr>
<tr>
<td>DBP (R), mm Hg</td>
<td>76.8±7.16</td>
<td>87.5±19.5</td>
<td>85.2±20.0</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>68.3±12.2</td>
<td>82.8±36.0</td>
<td>74.6±12.8</td>
</tr>
<tr>
<td>RPP (R)</td>
<td>8065±1512</td>
<td>10 934±1751</td>
<td>10 747±1847</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7±0.31</td>
<td>5.9±0.60</td>
<td>6.0±0.56</td>
</tr>
<tr>
<td>Smoking, cigarettes/d</td>
<td>15.0±8.7</td>
<td>15.0±14.9</td>
<td>14.3±11.6</td>
</tr>
<tr>
<td>No. of smokers</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>TC, mg/dl</td>
<td>195±16.6</td>
<td>253±27.34§</td>
<td>203±16.1</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>129±22.1</td>
<td>154±33.4§</td>
<td>109±13.2</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>43.4±6.81</td>
<td>50.6±11.6</td>
<td>39.0±10.5*</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>122±33.8</td>
<td>244±121t</td>
<td>357±152†</td>
</tr>
<tr>
<td>SBP (DP), mm Hg</td>
<td>122±16.5</td>
<td>136±30.1</td>
<td>143±27.8</td>
</tr>
<tr>
<td>DBP (DP), mm Hg</td>
<td>75.6±6.5</td>
<td>77.3±19.3</td>
<td>90.0±16.1</td>
</tr>
<tr>
<td>HR (DP), beats/min</td>
<td>82.5±19</td>
<td>77.9±18.0</td>
<td>78.4±14.6</td>
</tr>
<tr>
<td>RPP (DP)</td>
<td>10 068±1667</td>
<td>10 296±2228</td>
<td>11 133±2289</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; (R), rest; HR, heart rate; RPP, rate pressure products; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; and (DP), DP loading.

*P<0.05 vs MCHL. †P<0.01 vs control. §P<0.01 vs control. ¶P<0.01 vs HTG.

Selected Abbreviations and Acronyms
CAD = coronary artery disease
CAG = coronary angiography
HbA1c = hemoglobin A1c
HTG = normocholesterolemic hypertriglyceridemic
MBF = myocardial blood flow
MCHL = mixed combined hyperlipidemic
MVD = myocardial vasodilatation
PET = positron emission tomography
TC = total cholesterol
TG = triglyceride

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; (R), rest; HR, heart rate; RPP, rate pressure products; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; and (DP), DP loading.
coronary arteries (zero percent stenosis) were used in this study. Segments perfused by coronary arteries after percutaneous transluminal angioplasty were not included in this study, even if those coronary arteries were diagnosed as zero percent stenosis. To obtain input function, regions of interest were placed on the left ventricular cavity of each slice. Static [15N]ammonia images were also obtained from the PET study and analyzed visually by three independent specialists who had no other information on the patients. We then determined the MVD value as MVD = MBFDP/MBFR, where MBFDP is the MBF during DP loading and MBFR is the MBF at rest.

**Statistical Analysis**

The MBF at rest, MBF during DP loading, MVD, body weight, systolic blood pressure, diastolic blood pressure, height, body mass index, and lipid parameters in the three groups were compared using analysis of variance. Individual data were analyzed by the two-tailed Student’s $t$ test. Simple linear regression analysis was done between MVD and plasma lipid fractions, using the least-squares method. Then multivariate regression analysis was undertaken between MVD and factors considered using the least-squares method to examine which factors were independently related to MVD. Factors considered were TC, plasma TG level, HDL cholesterol, LDL cholesterol, systolic blood pressure, diastolic blood pressure, smoking habits, HbA1c, sex, and age. Two-tailed Student’s $t$ test was done to determine whether the regression coefficient was significantly different from zero. Values are expressed as the mean ± SD. A value of $P < .05$ was considered significant.

**Results**

**Hemodynamic and ECG Responses to DP Infusion**

There were no significant differences in systolic blood pressure at rest and during DP loading and rate pressure product among the three groups (Table 2). During DP loading, typical chest pain or chest oppression was observed in all of the patients with hypertriglyceridemia. Due to difficulty in recording ECG in the precordial leads on the PET study, detailed description of ECG response to DP was not possible in this study.

**MBF at Rest and During DP Loading**

Baseline MBF (mL min⁻¹ 100 g⁻¹ weight heart) in HTGs (76.0 ± 26.1) did not differ from that in control subjects (80.3 ± 38.5) and MCHLs (77.0 ± 9.30). MBF during DP loading in HTGs (202 ± 104) was comparable with that in control subjects (292 ± 166, $P = .153$), but in MCHLs (154 ± 54.0) was significantly lower than that in control subjects ($P < .01$).

**MVD**

When the hypertriglyceridemic subjects were considered as one group, MVD (2.30 ± 0.99, $n = 23$) was significantly lower than that in control subjects (3.73 ± 1.14, $P = .0048$). When these groups were considered separately, MVD in HTGs (2.69 ± 1.09, $n = 10$) was significantly lower than that in control subjects ($P = .038$), as was MVD in MCHLs (1.99 ± 0.73, $n = 13$; $P = .0038$). In comparing the two hypertriglyceridemic groups, MVD in MCHLs tended to be lower than that in HTGs, but not to a statistically significant degree ($P = .08$). There was no significant difference in MVD between patients with myocardial infarction (2.07 ± 0.78) and those without (2.36 ± 1.01). Because of the small number of study patents, there were not sufficient data for comparisons of sex variance.

**Relationship Between Plasma Lipid Fractions**

When the three groups were combined, there was a significant relationship between MVD and both plasma total TG concentration ($r = −.47, P < .01$; Fig 1, top) and plasma TC concentration ($r = −.55, P < .01$; Fig 1, bottom). When only the control and HTG groups were considered together, the relationship between MVD and plasma total TG became more prominent ($r = −.55, P < .05$; Fig 2, top), whereas the relationship between MVD and TC became insignificant (Fig 2, bottom). There was no significant relationship between MVD and plasma HDL cholesterol concentration. Multivariate regression analysis revealed that only plasma TG concentration ($F = 5.2, P < .05$) was independently related to MVD ($r = .69, P < .05$) among TC, LDL cholesterol, HDL cholesterol, TG, systolic blood pressure, diastolic blood pressure, HbA1c, smoking habits, and age (Table 3).

**Discussion**

**Reduced MVD in Hypertriglyceridemia**

One of the aims of the present work was to determine whether MVD in subjects with hypertriglyceridemia would be reduced in segments perfused by coronary arteries that had been proved to be normal by angiography. Results of this study did indeed show such a reduction, and furthermore, multivariate regression analysis showed that plasma TG concentration was independently related to the reduced MVD in these arteries. There are several possible explanations for this result. The diffuse but angiographically undetectable balanced macrovascular atherosclerosis that has been detected by intravascular ultrasound can be a factor for the reduction in MVD revealed in our study. Microcirculation abnormalities may also play a role in the observed reduction, as has been proposed in diabetic patients. The impairment in blood flow–mediated vasodi-
lation indicating endothelial dysfunction, as was suggested in hypercholesterolemics,16–22 may also be a factor. Although the principal pharmacological action of DP is acknowledged to be endothelium independent, it has been proposed that endothelial function partially contributes to the vasodilating action of DP.23 Therefore, impaired endothelial function may be involved in the reduced MVD in hypertriglyceridemics. Although a risk of CAD has been cited in hypertriglyceridemias,24–27 it is not yet clear whether endothelial function is impaired in hypertriglyceridemias independent of hypercholesterolemia.

Comparison of Hypercholesterolemia and Hypertriglyceridemia

Similar to our finding of reduced MVD in hypercholesterolemics without overt coronary stenosis,12 reduced MVD was seen in hypertriglyceridemia in angiographically normal coronary arteries. Although both hypertriglyceridemia and hypercholesterolemia appear to alter MVD, it is not clear whether the mechanisms are the same. As to this issue, several epidemiological investigations have shown that hypertriglyceridemia can be a risk factor for CAD24–28; furthermore, the concept of insulin resistance has emerged as a common cause underlying several risk factors for CAD.29 Since insulin resistance is usually associated with hypertriglyceridemia, the importance of hypertriglyceridemia as a risk factor for CAD has been cited, especially in relation to insulin resistance.29,30 Recent experiments on hypertriglyceridemic mice showed that severe atherosclerosis was seen in transgenic mice with a higher expression of the human apolipoprotein C-III gene compared with that in a relatively lower expression group.31 If one considers that reduced MVD in angiographically normal coronary arteries is an early manifestation of coronary atherosclerosis, those reports imply that the mechanism of the reduction of MVD associated with hypertriglyceridemia may be different from that in hypercholesterolemia.

Our results showed that MVD was significantly reduced in HTG, as well as in MCHL subjects. Furthermore, MVD in MCHL tended to be reduced compared with HTG subjects, with marginal significance. It is suggested that coexistence of hypercholesterolemia and hypertriglyceridemia would severely impair MVD. Of interest is that our result is similar to epidemiological data indicating that hypertriglyceridemia is an important risk factor in subjects with elevated cholesterol and results of recent animal experiments demonstrating more severe atherosclerosis in hypertriglyceridemic mice with lower expression of human apolipoprotein C-III gene that were fed a high-cholesterol diet as opposed to those who were not.32

Influence of Age and Sex Variance on MVD

Although a significantly reduced MVD in older normal subjects compared with that in young normal subjects was reported,33 there was no significant relationship between age and MVD in our study. With the narrow range of age among our subjects, it is natural that such an age-related variation would not occur. Previously, sex-specific variance of MVD in familial hypercholesterolemics and diabetics30 was shown. Because we selected our subjects purely on the parameters outlined previously rather than on family history, we cannot be certain of the duration of the hypertriglyceridemic state, although we can speculate that the duration of that state may not have been sufficient for sex variations to become apparent. Further investigation should be done on this point in relation to familial hypertriglyceridemia.

Measurement of MBF Using PET and [13N]Ammonia

We used the two-compartment [13N]ammonia tracer kinetic model to determine MBF, using dynamic PET and [13N]ammonia,13,14 because this model has been well validated and frequently used in the assessment of MBF or MVD.2,5,10,12,33–40 Recently, Hutchins et al41 developed a three-compartment model as another model to measure MBF, using PET and [13N]ammonia. The main difference between the two models is whether or not myocardial metabolism of [13N]ammonia should be addressed. Because myocardial metabolism of
Myocardial Vasodilatation in Hypertriglyceridemias

[13N]ammonia can be negligible within the first 90 seconds after its administration, accuracy in measuring MBF is assured.

Diagnosis of Coronary Arterial Stenosis

In this study, diagnosis of CAD or normal coronary arteries was made by visual inspection by three independent specialists, which is a conventionally acceptable practice. However, this means may not allow the diagnosis of a minor degree of diffuse coronary atherosclerosis with certainty, as has been reported by Mintz et al. Application of quantitative coronary artery arteriography or intravascular ultrasound would be more helpful to identify whether reduced MVD is due to a minor degree of diffuse coronary atherosclerosis or another cause. Quantitative methods usually present difficulties in establishing good automated software to exclude uncertainties with this type of analysis. Therefore, it would appear that intravascular ultrasound should be the more useful means to address this question, and further studies should address this point.

Cardiac Normality in Control Subjects

It is difficult to justify the performance of CAG on asymptomatic normal subjects. For this reason, we assessed cardiac normality on the basis of absence of risk factors for CAD rather than on results of cardiac catheterization, as discussed by Rozanski et al. Therefore, even if CAG was not undertaken, we consider our control subjects to be appropriate. Furthermore, given the high diagnostic accuracy of static myocardial PET imaging for CAD, it can be concluded that normal results of PET imaging would indicate normal anatomy and function of coronary arteries in asymptomatic subjects without coronary risk factors or chronic disease.

Conclusion

MVD was decreased in patients with hypertriglyceridemia without overt coronary stenosis. Hypertriglyceridemia was independently related to this abnormality.

Acknowledgments

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References


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