RELATIONSHIP BETWEEN CORONARY ARTERY STENOSIS AND RENAL DYSFUNCTION : COMPARISONS OF MULTIDETECTOR-ROW CT CORONARY ANGIOGRAMS WITH ESTIMATED GLOMERULAR FILTRATION RATES

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Abstract
The relationship between chronic kidney disease (CKD) and cardiovascular diseases has recently received considerable focus. We compared estimated glomerular filtration rates (eGFR) with coronary stenosis visually assessed by CT coronary angiography (CTCA) in 578 patients (285 men, 293 women ; average age, 68 y). Among these, 520 assessable patients were classified according to stenosis rates of <25%, 25-49%, 50-74% and ≥75% as normal coronary arteries (n=232), slight (n=102), moderate (n=70) and severe (n=116) stenosis, respectively. They were also classified by eGFR (ml/min/1.73 m^2) values of ≥90, 60-90 and <60 as having normal (n=119) or slight (n=314) renal dysfunction and CKD (n=87), respectively. The average (±standard deviation ; SD) eGFR values of the groups with normal arteries, slight, moderate and severe stenosis were 83.39±20.49, 78.54±18.37, 74.05±18.75 and 68.78±17.53, respectively. The ratios of patients with >50% stenosis and who had previously undergone percutaneous coronary intervention (PCI) among the groups with normal and slight renal dysfunction and CKD were 23.53% and 9.24%, 34.08% and 14.97%, and 59.77% and 31.03%, respectively. Our findings indicated that CKD might cause coronary stenosis to progress, and that eGFR combined with CTCA findings will comprise a useful screening modality for coronary stenosis.

Key words : CKD, renal dysfunction, eGFR, coronary stenosis, CT coronary angiography

Introduction

Chronic kidney disease (CKD) is a lifestyle-related disease similar to metabolic syndrome, and it is an important condition in preventive medicine as it is a considerable risk factor for cardiovascular disease (CVD). Many reports have shown that high rates of CKD are associated with the development and mortality of myocardial infarction, congestive heart failure, and cerebral infarction[1-11]. Furthermore, slight renal dysfunction is also associated with CVD[1,11]. Thus, CKD should be prevented and treated like conventional coronary risk factors such as hypertension, diabetes mellitus, and hyperlipidemia to prevent CVD. Computed tomography (CT) cor-

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onary angiography (CTCA) using multidetector-row CT (MDCT) has recently become a popular diagnostic tool for imaging the coronary arteries. Low invasiveness and excellent quality images are features of CTCA, which along with conventional coronary angiography (CAG) equals the utility of coronary imaging in diagnosing diseases of the coronary arteries[12-27]. Estimated glomerular filtration rate (eGFR) is a standard modality for diagnosing CKD that depends on age, serum creatinine and sex[28-31]. Here, we compared eGFR values with findings of coronary stenosis determined by CTCA using MDCT, and considered the relationship between progressive coronary stenosis and renal dysfunction. We examined whether slight renal dysfunction is significantly associated with coronary stenosis lesions in addition to CKD, whether CKD and slight renal dysfunction together cause the progression of coronary stenosis, and whether the combination of eGFR and CTCA findings comprise a useful screen for significant coronary stenosis in patients with renal dysfunction.

Materials and methods

Patients

We enrolled 578 consecutive patients (male/female, 285/293 ; average age±standard deviation (SD) of all patients, 68.0±10.7 y ; men, 66.4±11.5 y ; women, 69.5±9.6 y) who underwent CTCA using 16- or 64-row CT (Aqulion, Toshiba, Tokyo, Japan) between June 15th, 2004 and October 15th, 2009. All male and female patients were respectively classified by age decade as follows : 20 s (n=1 each), 30 s (n=4 and n=0), 40 s (n=19 and n=8), 50 s (n=57 and n=36), 60 s (n=71 and n=82), 70 s (n=107 and n=122), 80 s (n=24 and n=44) and 90s (n=2 and n=0). They comprised 49 patients with old myocardial infarction, 320 with angina pectoris, 63 at silent high risk with over three conventional coronary risk factors such as hypertension, hyperlipidemia, diabetes mellitus, family history of coronary vascular disease and smoking, 126 with atypical chest pain without detectable ischemic change and 20 with other conditions.

Assessment of coronary artery stenosis lesion using CTCA

Coronary artery stenosis was assessed from CTCA images using a Workstation with the analyzing coronary artery software, ZIOSOFT M900 (Amin, Tokyo, Japan), volume rendering and curved multiplanar reformation (curved-MPR). Images were assessed for coronary stenosis at our hospital by the consensus of two physicians and one radiologist. All patients were classified into groups according to rates of stenosis in the major coronary arteries that were amenable to percutaneous coronary intervention (PCI) as follows. Normal coronary arteries, slight, moderate and severe stenosis were classified as stenosis of <25%, 25-49%, 50-74% and ≥75%, respectively (Fig. 1). Patients with previously detected stenosis or who had already undergone PCI before CTCA were considered as having severe stenosis regardless of the CTCA findings. To examine the relationship between coronary artery stenosis and eGFR, normal coronary arteries, and slight, moderate and severe stenosis were scored by CT as 1, 2, 3 and 4, respectively. These CT scores were summed for each the

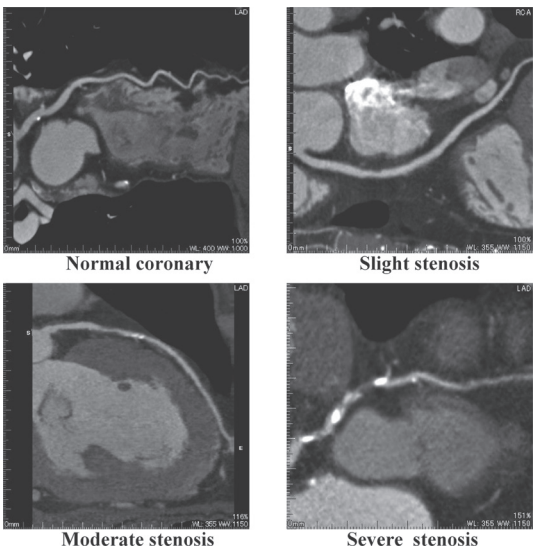

Fig. 1. Curved-MPR images of coronary arteries with coronary stenosis evaluated with CTCA using MDCT. Stenosis rates of <25%, 25-49%, 50-74% and ≥75% were classified as normal coronary, slight, moderate and severe stenosis, respectively

groups according to renal function. We also compared the average eGFR values of the groups according to degree of coronary stenosis, and the ratios of patients with each degree of stenosis according to renal function.

Calculation of eGFR and patient classification according to renal function

The standard for evaluating GFR is inulin clearance, which is very difficult to measure. Therefore, eGFR (ml/min/1.73 m^2 ; units are omitted from subsequent values, which are shown as numbers) is used as a substitute for GFR in routine clinical practice. We calculated eGFR values in assessable patients using a portable computer (J Pocket Clearance 2008, Kureha, Tokyo, Japan) that measures Japanese eGFR[31], and we also measured serum creatinine using an enzymatic method and an automated analytical instrument (80FRNEO2, Toshiba, Tokyo, Japan) before performing CTCA. We classified CKD stage in assessable patients according to eGFR values of ≥90, 60–90 and <60 as having normal renal function equivalent to CKD stage 1 or high risk, slight renal dysfunction equivalent to CKD stage 2 and CKD equivalent to CKD stage 3–5, respectively. These patients were also grouped in more detail according to eGFR values. We compared the average CT score in each of the renal function groups, and determined the ratios of patients with >50% stenosis and PCI according to renal function or eGFR value.

Statistical analysis

Data were analyzed using Stat View 5.0 or Windows Excel 2003 software. Average differences between two groups were compared using a t-test when the analysis of variance (ANOVA) indicated significant differences in all populations. Significant differences in ratios between two groups were compared using Ryan's method after significance in all populations was determined using the χ^2 test with a contingency table. A value of $p<0.05$ indicated significant difference.

Results

Diagnosing coronary artery stenosis using CTCA

Among all 578 patients, coronary stenosis could not be evaluated in 40 cases due to significant calcification, motion artifacts and insufficient enhancement of the coronary artery, and 18 had peripheral artery stenosis or lateral branch stenosis that would not be amenable to PCI. These 58 patients were considered as not assessable. Thus, 520 assessable patients comprised 232 with normal coronary arteries, 102 with slight, 70 with moderate and 116 with severe stenosis.

Evaluation of average eGFR values according to coronary stenosis

As eGFR value is dependent on age, we computed the correlation coefficients between age and CT score and between age and eGFR value to investigate the relationship between age and coronary stenosis and whether eGFR is associated with coronary stenosis independently of age. The correlation coefficients between age and CT score were 0.25, 0.24 and 0.34, in all of the 520 assessable patients regardless of sex, in 257 men of them and in 263 women of them, respectively. Similarly, the correlation coefficients between age and eGFR value were −0.38, −0.31 and −0.48, in the 520 assessable patients, in 257 men of them and in 263 women of them, respectively. These findings indicated that age does not correlate with either CT score or eGFR value. Moreover, the correlation coefficients between eGFR value and CT score were −0.29, −0.26 and −0.33, in those patients regardless of sex, in the 257 men and in the 263 women, respectively.

The average±SD of the eGFR values of the groups with normal coronary arteries, and with slight, moderate and severe stenosis were 83.39±20.49, 78.54±18.37, 74.05±18.75, and 68.78±17.53, respectively (Fig. 2). The SD values were large, indicating wide variation in the eGFR values for each of the stenosis groups. Nevertheless, increasing coronary stenosis rates were associated with decreasing average eGFR values. The average±SD of the eGFR values in 85 patients who had undergone previous PCI and who were thus considered to have severe stenosis was 67.79±18.26, which was smaller than in the other groups with less stenosis. Significant differences were found between the groups with normal coronary arteries and slight, moderate and severe stenosis, and between those

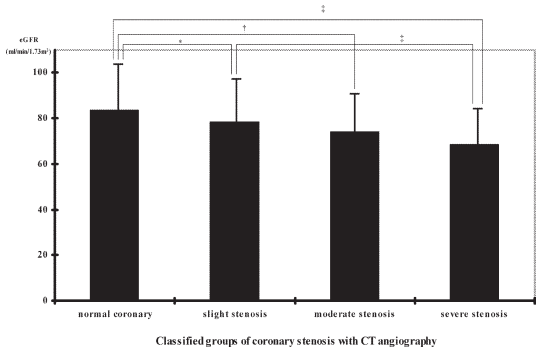

Fig. 2. Relationship between average eGFR value and coronary stenosis. Average eGFR value decreased with increasing degree of stenosis. Significant differences between normal coronary and slight, moderate and severe stenosis groups, and between slight and severe stenosis groups, respectively (ANOVA ; *, $p=0.04$; †, $p=0.0008$; ‡, $p<0.0001$).

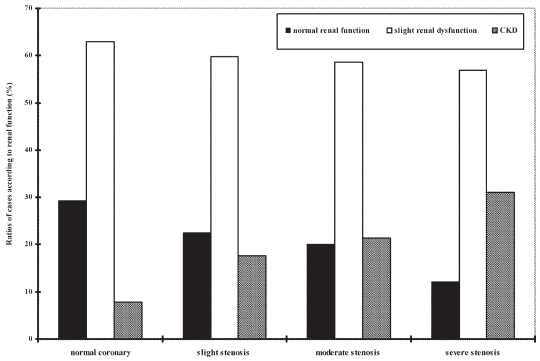

Fig. 3. Comparison of renal function in each coronary stenosis group. Increasing coronary stenosis severity was associated with lower ratios of normal renal function and higher ratios of CKD. Ratios of CKD significantly differed between groups with normal coronary arteries and with severe stenosis (Ryan's method ; $p<0.05$).

with slight and severe stenosis (ANOVA ; $p=0.04$, 0.0008, <0.0001 and <0.0001, respectively). Thus, the eGFR values varied considerably in each of the stenotic groups, but eGFR was associated with coronary stenosis independently of age.

Comparison of renal function in each group with coronary stenosis

Figure 3 compares patients based on renal function in each the coronary stenosis groups. In the group with normal coronary arteries, the ratios of patients with normal renal function, slight renal dysfunction and CKD were 29.31% (68/232), 62.93% (146/232) and 7.76% (18/232), respectively. The ratios in the group with slight stenosis were 22.55% (23/102), 59.80% (61/102) and 17.65% (18/102), respectively. In the group with moderate stenosis, these ratios were 20.00% (14/70), 58.57% (41/70) and 21.43% (15/70), respectively, and in that with severe stenosis, 12.07% (14/116), 56.90% (66/116) and 31.03% (36/116), respectively. These findings indicate that more severe coronary stenosis was associated with an increased ratio of patients with CKD. Significant differences in the ratios of CKD were found between the groups with normal coronary arteries and with severe stenosis (Ryan's method ; $p<0.05$).

Comparison of average CT scores according to renal function

The 520 assessable patients comprised 119 with normal renal function, 314 with slight renal dysfunction and 87 with CKD. They were also classified by eGFR values as follows. The numbers of patients with eGFR values of 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 and ≥130 were 1, 10, 30, 46, 87, 128, 99, 56 35, 16, 7 and 5, respectively (Table 1). Figure 4 shows that the average±SD of CT scores of the groups with normal renal function, slight renal dysfunction and CKD were 1.78±1.05, 2.09±1.20 and 2.79±1.19, respectively. Significant differences were found between the groups with normal renal function and slight dysfunction and with CKD, and between the groups with slight dysfunction and with CKD (ANOVA ; $p=0.02$, <0.0001, <0.0001, respectively). Coronary artery stenosis had obviously progressed in the patients with CKD. Table 1 shows that the average±SD of CT scores value in each group according to eGFR values of 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 and ≥130 were 4.00±0.00, 3.20±0.75, 2.83±1.24, 2.65±1.20, 2.32±1.25, 2.09±1.22, 1.88±1.07, 1.93±1.08, 1.74±1.13, 1.75±0.90, 1.43±0.73 and 1.00±0.00, respectively. As the eGFR value decreased, the CT score value increased, indicating that coronary stenosis progresses with increasing renal dysfunction.

Table 1. Average ± SD of CT scores, Ratios of patients with >50% stenosis and of those who had previously undergone PCI according to eGFR values.

eGFR values	20 marks (n=1)	30 marks (n=10)	40 marks (n=30)	50 marks (n=46)	60 marks (n=87)	70 marks (n=128)	80 marks (n=99)	90 marks (n=56)	100 marks (n=35)	110 marks (n=16)	120 marks (n=7)	≥130 (n=5)
Average±SD of CT scores	4.00 ±0.00	3.20 ±0.75	2.83 ±1.24	2.65 ±1.20	2.32 ±1.25	2.09 ±1.22	1.88 ±1.07	1.93 ±1.08	1.74 ±1.13	1.75 ±0.90	1.43 ±0.73	1.00 ±0.00
Ratios of patients with >50% stenosis	100.00% (1/1)	80.00% (8/10)	60.00% (18/30)	52.17% (24/46)	43.68% (38/87)	34.38% (44/128)	25.25% (25/99)	30.36% (17/56)	20.00% (7/35)	18.75% (3/16)	14.29% (1/7)	0.00% (0/5)
Ratios of patients with PCI	100.00% (1/1)	40.00% (4/10)	40.00% (12/30)	21.74% (10/46)	22.99% (20/87)	14.84% (19/128)	8.08% (8/99)	10.71% (6/56)	11.43% (4/35)	6.25% (1/16)	0.00% (0/7)	0.00% (0/5)

Decreasing eGFR values are associated with higher CT scores indicating concurrent progression of renal dysfunction and coronary stenosis. Ratios of both are high in all groups with eGFR values <60. These ratios in the patients with eGFR values of 60 and 70 were also high.

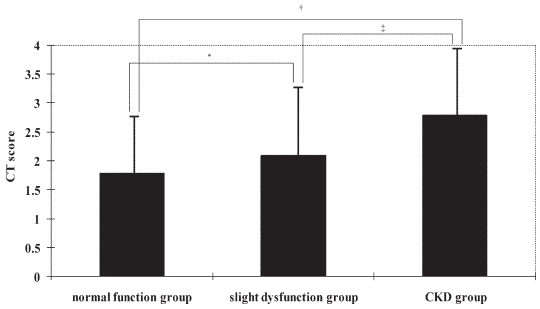

Fig. 4. Comparison of averages ± standard deviations (SD) of CT scores according to renal function. The average ± SD of CT scores of groups with normal renal function, slight renal dysfunction and CKD are 1.78 ± 1.05, 2.09 ± 1.20 and 2.79 ± 1.19, respectively. Significant differences were found between groups with normal function and slight dysfunction, with normal function and CKD, and with slight dysfunction and CKD, respectively (ANOVA ; *, $p=0.02$; †, $p<0.0001$; ‡ : $p<0.0001$). Coronary artery stenosis progressed particularly in patients with CKD.

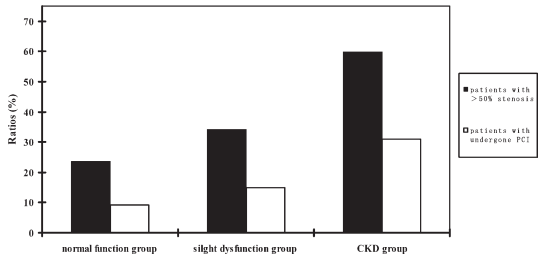

Fig. 5. Ratios of patients with >50% stenosis and PCI in renal function groups. The ratios of patients with >50% stenosis in the groups with normal function, slight dysfunction and CKD are 23.53%, 34.08% and 59.77%, respectively. The ratios of patients who had previously undergone PCI in each group are 9.24%, 14.97%, and 31.03%, respectively. The ratios of patients with >50% stenosis and of those who had previously undergone PCI were significantly higher in the CKD group than in any other group (Ryan's method ; $p<0.05$).

Ratios of patients with >50% stenosis and PCI according to renal function

Figure 5 shows ratios of patients with >50% stenosis (70 and 116 with moderate or severe stenosis, respectively) according to renal function. These ratios in the groups with normal renal function, slight dysfunction and CKD were 23.53% (28/119), 34.08% (107/314) and 59.77% (51/87), respectively. The ratios of patients who had previously undergone PCI were 9.24% (11/119), 14.97% (47/314) and 31.03% (27/87), respectively. The ratios of patients with >50% stenosis and of those who had undergone previous PCI were significantly higher in the group with CKD than in the other two groups (Ryan's method ; $p<0.05$).

Ratios of patients with >50% stenosis and PCI according to eGFR values

Table 1 shows that the ratios of patients with >50% stenosis according to eGFR values of 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 and ≥130 were 100.00% (1/1), 80.00% (8/10), 60.00% (18/30), 52.17% (24/46), 43.68% (38/87), 34.38% (44/128), 25.25% (25/99), 30.36% (17/56), 20.00% (7/35), 18.75% (3/16), 14.29% (1/7) and 0.00% (0/5), respectively. The ratios of those who had undergone previous PCI were 100.00% (1/1), 40.00% (4/10), 40.00% (12/30), 21.74% (10/46), 22.99% (20/87), 14.84% (19/128), 8.08% (8/99), 10.71% (6/56), 11.43% (4/35),

6.25% (1/16), 0.00% (0/7) and 0.00% (0/5), respectively. The ratios of patients with >50% stenosis and of those who had undergone previous PCI case were high in all groups with eGFR values <60 as well as in patients with eGFR values of 60 or 70.

Discussion

We investigated the relationship between the progression of coronary stenosis and eGFR. We found that rates of coronary stenosis determined by CTCA increased as renal function decreased along with lower average eGFR values. In addition, the ratio of CKD increased with higher severity of coronary stenosis. The ratios of patients with >50% stenosis and of those who had previously undergone PCI were significantly higher in the group with CKD than in the other groups classified according to renal function. These results indicate that if renal dysfunction progresses to CKD, then the severity of coronary stenosis also progresses. Moreover, these ratios in groups with eGFR values of 60 or 70 were also higher and the average±SD of 85 patients who had previously undergone PCI was 67.79±18.26. Therefore, the progression of coronary stenosis might also be associated even with slight renal dysfunction. Many investigators have described a relationship between CVD and CKD. These reports indicate a higher risk of developing and dying of CVD, a higher frequency of repeated cardiovascular events, and higher frequencies of fatal ventricular arrhythmia and of heart pump disorders among patients with CKD. However, only a few reports have described a relationship between CKD and the progression of coronary stenosis as a prelude to the appearance of cardiovascular events, and only a few reports have presented evidence of CKD among Japanese patients. This study suggests that CKD participates in not only the appearance and mortality of CVD but also in the progression of coronary stenosis, which is the main factor in CVD. Therefore, we believe that this notion has considerable significance. Our results suggest that CKD represents a significant risk factor for CVD in terms of the progression of coronary stenosis, and that active intervention for CKD is indispensable for the prevention of CVD. Several reports have indicated that treating conventional hypertension, diabetes mellitus and hyperlipidemia inhibits CKD progression and possibly the decrease in GFR[32-37]. These findings are supported by the fact that risk factors for CKD and for CVD, namely, increasing age, hypertension, diabetes mellitus, hyperlipidemia and smoking, closely overlap. Thus, the measures for treating CKD are exactly those of aggressively treating the conventional coronary risk factors of hypertension, diabetes mellitus and hyperlipidemia ; that is, applying a strict antihypertensive approach, angiotensin inhibitors, decreasing proteinuria, and maintaining HbA1c at <6.5% and LDL-cholesterol at <120 mg/dl. The Japanese eGFR is considered to be lower than that in other countries, perhaps not only because of physical and race differences, but also because of the traditional Japanese diet. The amount of salt intake per day among Japanese is 11-13 g, which is higher than the 5-10 g of intake by Western peoples. Consequently, we believe that such long-term salt intake influences renal function among Japanese. Thus, to take measures against CKD in Japan requires the accumulation of evidence about the relationship between CKD and CVD among Japanese, to establish examination and treatment guidelines for CKD, to establish dietary guidelines for Japanese based on the evidence, and to extensively educate the public. We found that the ratios of patients with severe coronary stenosis according to CTCA were rather high not only among those with CKD but also among those with slight renal dysfunction indicated by eGFR values of 60 or 70. We therefore suggest that when patients have slight renal dysfunction, conventional risk factors or chest pain should be screened and risk assessed by CTCA. To evaluate coronary stenosis as the main factor of CVD is important for preventing its development. Thus, evaluating coronary lesions using minimally invasive CTCA and measuring eGFR could both play a significant role in the prevention of CVD. We believe that if eGFR is put into clinical practice as a routine examination, combining the results with those of CTCA will comprise a useful tool for detecting coronary stenosis.

Conclusions

We compared eGFR values with CTCA findings of cor-

onary stenosis in 578 patients using MDCT. The results suggested that a greater severity of CKD is associated with and participates in the progression of coronary stenosis. Furthermore, eGFR values combined with CTCA findings will serve as a useful tool for detecting coronary stenosis.

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