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의학석사 학위논문

Assessing Impact of High-Dose Pitavastatin on Carotid Artery Elasticity with Speckle-Tracking Imaging

고용량 pitavastatin이 경동맥 탄성에 주는 영향을 반점 추적 영상을 이용하여 분석한 연구

2017년 02월

서울대학교 의과대학

임상의과학과 석사과정

김 지 혜

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지도교수 김 용 진

이 논문을 의학석사 학위논문으로 제출함

2016년 10월

서울대학교 의과대학

임상의과학과 석사과정

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김지혜의 의학석사 학위논문을 인준함

2016년 12월

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Abstract

Background: Two-dimensional speckle-tracking strain imaging has been introduced for the precise assessment of arterial mechanics. The objective of this study was to evaluate the short-term effects of pitavastatin on carotid artery elasticity measured by speckle tracking methods.

Methods: This study included 30 statin-naïve patients (age, 61.6 ± 7.6 years; 26.7% male) with hypercholesterolemia. Circumferential carotid artery strain (CAS) was measured using speckle-tracking imaging before and after 3 months of high-dose pitavastatin treatment (4 mg daily).

Results: After 3 months, circumferential CAS was significantly increased compared to baseline (from 2.73 ± 1.17% to 3.27 ± 1.53%, p = 0.029). Among conventional carotid elasticity metrics, strain measured by B-mode improved significantly after statin therapy. No significant change in carotid intima-media thickness was observed after pitavastatin treatment (from 0.73 ± 0.18 to 0.71 ± 0.16 mm, p = 0.913).

Conclusions: Short-term treatment with high-dose pitavastatin improved carotid artery elasticity measured by speckle-tracking methods. These speckle-tracking imaging-based measurements may allow the early noninvasive assessment of favorable effects of medical intervention in patients with hypercholesterolemia.

Key words: pitavastatin; carotid artery; elasticity; speckle-tracking imaging

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Lists of abbreviations

LDL-C low-density lipoprotein cholesterol

HDL-C high-density lipoprotein cholesterol

SBP systolic blood pressure

DBP diastolic blood pressure

ROI regions of interest

CCA common carotid artery

CAS carotid artery strain

IMT intima-media thickness

Introduction

Atherosclerosis is a growing problem worldwide, leading to an increased risk of cardiovascular events, including stroke, myocardial infarction, and heart failure (HF),[1] The loss of arterial elasticity has been suggested as an early marker of atherosclerosis and a strong predictor of subsequent risk of cardiovascular diseases.[2] Evidence is also emerging that treatment to improve the arterial compliance can potentially reduce cardiovascular morbidity and mortality.

Statins have been the mainstay of therapy for atherosclerotic cardiovascular diseases, dramatically reducing mortality and morbidity. There are several lines of evidence suggesting that statins can exhibit pleiotropic effects on cardiovascular system in addition to their cholesterol-lowering properties. Previous studies showed that atorvastatin treatment was associated with better endothelium-dependent vasodilatation.[3,4] Other studies also demonstrated that statins improved carotid artery stiffness measured by ultrasound, providing the potential to extend the benefits of statin therapy to asymptomatic subjects with early atherosclerosis.[5,6] However, these results were based on the measurements of changes in carotid diameter obtained by B-mode ultrasound, which is a one-dimensional approach having several limitations in accurately assessing carotid elasticity, such as angle dependency.[7,8] As part of the efforts to overcome the limitations of conventional techniques, speckle-tracking imaging has been introduced as a

novel technology allowing the assessment of vascular mechanics without angle dependency.[8] However, its utility in evaluating the effect of statin on carotid artery elasticity has not been studied until recently.

Hence, we sought to evaluate the impact of short-term treatment with high-dose pitavastatin on the parameters of carotid arterial elasticity measured by 2D speckle-tracking strain imaging.

Methods

Study population and design

From June 2014 to June 2015, 30 patients with hypercholesterolemia who were candidates for statin treatment according to the National Cholesterol Education Program: Adult Treatment Panel III[12] were prospectively recruited. To be eligible, participants were required to meet the following criteria: (1) age from 40 to 80 years, (2) statin-naive subjects, and (3) low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL with ≥2 major risk factors for coronary heart disease (CHD) or LDL-C≥160 mg/dL with <2 risk factors. Major risk factors for CHD include: (1) ≥45 years of age for men or ≥55 years of age for women, (2) family history of premature CHD (CHD in male first-degree relative <55 years or in female first-degree relative <65 years), (3) current cigarette smoking, (4) blood pressure (BP) ≥140/90 mmHg or on anti-hypertensive medication, and (5) high-density lipoprotein cholesterol (HDL-C) <40 mg/dL. Exclusion criteria were: (1) hospitalization for acute coronary syndrome or cerebrovascular disease within the previous 2 months, (2) the use of statin or other lipid-lowering medication within the previous 3 months, (3) impaired hepatic function or a history of liver disease, (4) chronic renal failure, (5) a history of malignancy, (6) any known contraindication to statin therapy, such as statin allergy, cyclosporin use, pregnancy, breastfeeding, myopathy, or lactose intolerance, and (7) failure to obtain informed consent from participants.

All subjects received pitavastatin 4mg daily for 3 months. Study assessments were performed at baseline and 3 months after statin therapy, which consisted of medical history including adverse events, physical examination, BP measurements, carotid ultrasound, and laboratory tests including lipid profiles, liver and kidney function tests, cardiac troponin I, and high-sensitivity C-reactive protein (hs-CRP). The study protocol was approved by our institutional review board and is in accordance with the Declaration of Helsinki. All study subjects provided written informed consent to participate in this study.

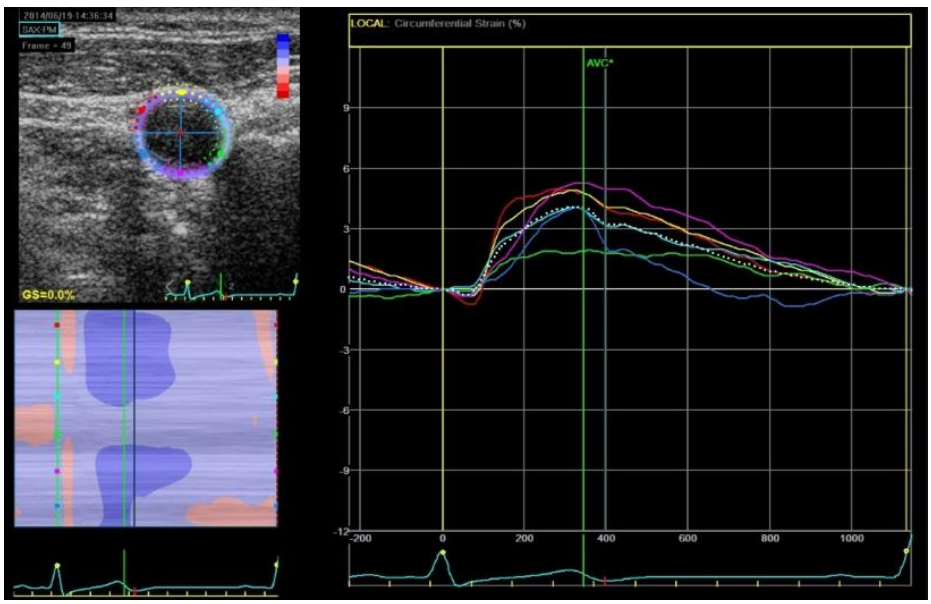

Figure 1. Representative example of measurement of circumferential CAS by speckle-tracking imaging.

Carotid ultrasound

Ultrasound images were acquired with a GE Vivid E9 system (GE Healthcare) and a 7.5-MHz linear 2D array transducer. The distal left common carotid arteries (CCA) were imaged 10-mm inferior to the carotid bulb in transverse sections with electrocardiography-gating over at least 3 cardiac cycles. Images were transferred to a workstation equipped with 2D strain software (EchoPAC version 201; GE Healthcare). We performed carotid arterial strain (CAS) analysis using speckle-tracking as previously described.[7, 13-15] Briefly, all the regions of interest (ROI) were placed to cover the cross-sectional area of the CCA wall. The software automatically detected frame-to-frame movement of each speckle on the CCA wall during the cardiac cycle. The CCA wall was equally divided into 6 segments and each segment was analyzed individually. From each time-strain curve for all 6 segments, the global circumferential peak systolic strain (%) was determined. Systolic (SBP) and diastolic BP (DBP) were measured before and after the carotid ultrasound examination and then averaged. Speckle-tracking-derived stiffness index (β_2) was calculated as follows: β_2 = ln(SBP/DBP)/strain by speckle-tracking.[8,16] Figure 1 shows a typical example of circumferential CAS curves.

Conventional carotid artery elasticity metrics and intima-media thickness (IMT) were also assessed using B-mode ultrasound as previously described.[5] Briefly, systolic (Ds) and diastolic diameters (Dd) were measured and averaged over 3 cardiac cycles. Elasticity variables were calculated as follows: strain by B-mode (%) = (Ds-Dd)/Dd, classic stiffness index (β1) = ln(SBP/DBP)/strain by B-mode ultrasound, and distensibility =

1/[ln(SBP/DBP)/strain by B-mode ultrasound × IMT]. Carotid IMT was defined as the distance between the leading edges of the first and second echogenic lines, representing the lumen-intimal interface and the upper layer of the adventitia, respectively.

Statistical Analysis

The values are expressed as the mean (± standard deviation) or median (interquartile ranges) as appropriate. The paired *t*-test was used to study the change in variables between baseline and 3 months after statin therapy. We used intra-class correlation coefficients and Bland-Altman analyses to assess inter- and intra-observer variabilities. Two-sided p values <0.05 were considered statistically significant. All analyses were performed using SPSS version 22.0 (IBM Co., Armonk, NY, USA).

Results

The mean age was 62 ± 8 years and female predominance was observed (73.3%, [22/30]) in this study. Nineteen patients (63%) had hypertension, 4 patients (13%) had diabetes, 2 patients (7%) had history of previous cerebrovascular disease. None of the patients had coronary artery disease. Of the patients, 15 (50%) were taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), 8 (27%) were taking beta-blockers (BB) and 9 (30%) were taking calcium-channel blockers (CCB). The medication types and doses were not changed before and after 3 months of pitavastatin treatment. Initial laboratory analysis showed no abnormal findings, except for elevated total cholesterol and LDL-C levels. Clinical and laboratory characteristics at baseline and at follow-up are summarized in Table 1. Total cholesterol and LDL-C levels significantly reduced after 3 months of pitavastatin treatment, compared to baseline. The level of triglyceride was also significantly reduced at 3 months. There were no significant changes in the values of other laboratory values including cardiac troponin I and hs-CRP.

Table 1. Clinical and laboratory features before and after pitavastatin treatment

	Baseline	3 months	*p* value
Clinical data			
Body mass index, kg/m^2	25.5 ± 3.7	25.7 ± 3.8	0.273
Body surface area, m^2	1.69 ± 0.15	1.68 ± 0.15	0.109
Systolic blood pressure, mmHg	123 ±10	123 ± 8	0.703
Diastolic blood pressure, mmHg	77 ±10	78 ±9	0.528
Heart rate, bpm	72 ± 8	71 ±3	0.913
Laboratory data			
Total cholesterol, mg/dL	245.2 ± 19.1	159.2 ± 18.9	<0.000
Low-density lipoprotein cholesterol, mg/dL	167.8 ± 17.1	84.5 ± 17.6	<0.001
High-density lipoprotein cholesterol, mg/dL	55.1 ± 9.0	57.7 ± 10.8	0.235
Triglyceride, mg/dL	157.6 ±75.1	128.1 ±43.9	0.014

Aspartate Aminotransferase, IU/L	26.5 ± 9.0	26.4 ± 8.9	0.945
Alanine Aminotransferase, IU/L	31.2 ± 18.0	30.8 ± 17.5	0.879
Bilirubin, g/dl	0.7 ± 0.3	0.6 ± 0.2	0.005
Blood urea nitrogen, mg/dL	14.4 ± 4.0	14.0 ± 4.0	0.606
Creatinine, mg/dL	0.83 ± 0.16	0.78 ± 0.18	0.006
Cardiac troponin I, ng/mL	0.01 (0.01-0.01)	0.01 (0.01-0.01)	1.000
High-sensitivity C-reactive protein, mg/dL	0.12 (0.03-0.26)	0.14 (0.04-0.26)	0.117

Values are given as mean ± standard deviation, except for cardiac troponin I and high-sensitivity C-reactive protein given as median (interquartile range).

Effect of pitavastatin on carotid artery elasticity parameters

Effects of high-dose pitavastatin on carotid artery elasticity parameters are shown in Table 2. After 3 months of pitavastatin treatment, speckle-tracking-derived circumferential CAS significantly increased (from 2.73 ± 1.17% to 3.27 ± 1.53%, $p = 0.029$) and β_2 index significantly decreased compared to baseline (from 0.20 ± 0.09 to 0.17 ± 0.08, $p = 0.048$). Among conventional carotid elasticity metrics, only B-mode ultrasound-derived strain, but not classic β_1 index nor distensibility, improved significantly after pitavastatin therapy (from 7.55 ± 2.92% to 8.99 ± 3.32%, $p = 0.047$). No significant change in carotid IMT was observed from baseline. Figure 2 shows the change in individual circumferential CAS and β_2 index values for each patient.

Table 2. Carotid ultrasound parameters before and after pitavastatin treatment

	Baseline	3 months	*p* value
Elasticity parameters by speckle-tracking method			
Circumferential CAS, %	2.73 ± 1.17	3.27 ± 1.53	0.029
Stiffness index (β_2)	0.20 ± 0.09	0.17 ± 0.08	0.048
Elasticity parameters by B-mode ultrasound			
Strain (fractional diameter change), %	7.55 ± 2.92	8.99 ± 3.32	0.047
Stiffness index (β_1)	0.07 ± 0.03	0.06 ± 0.04	0.217
Distensibility	24.5 ± 11.5	31.2 ± 18.3	0.091
Intima-media thickness, mm	0.73 ± 0.18	0.71 ± 0.16	0.913

Values are given as mean ± standard deviation. CAS = carotid artery strain.

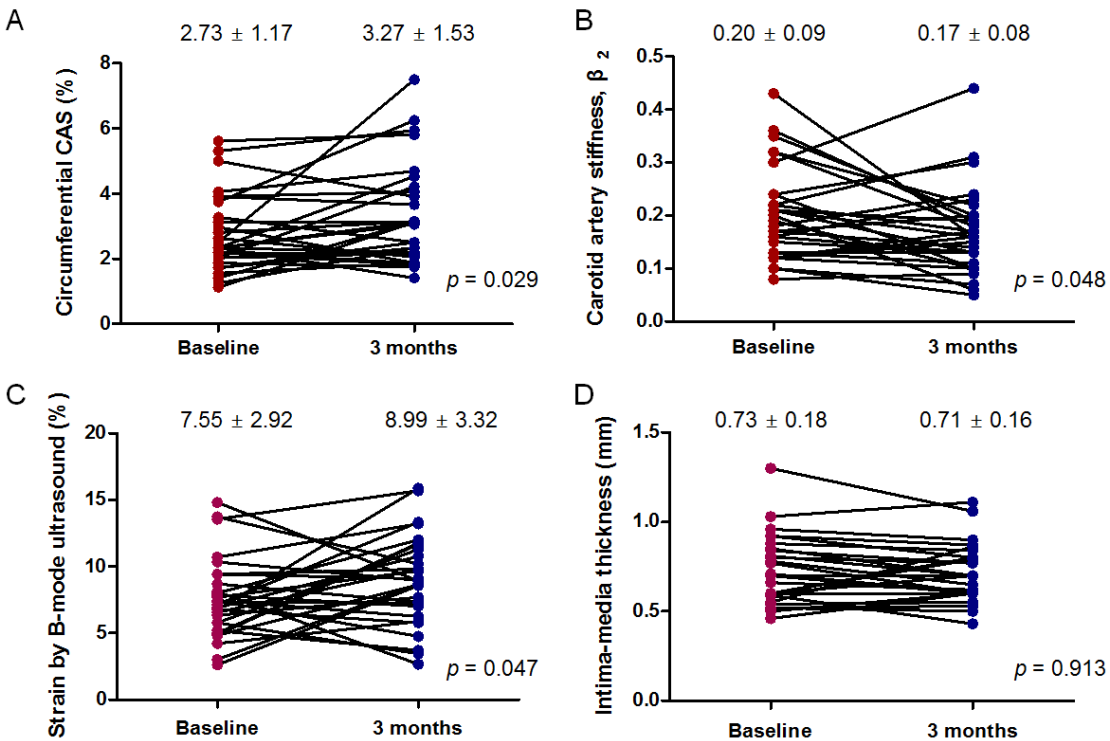

Figure 2. Plot of individual values of carotid artery variables at pre- and post-treatment

The changes in circumferential CAS (A), stiffness index (β_2) (B), strain by B-mode ultrasound (C), and IMT (D)

Measurement reproducibility

Intra- and inter-observer variabilities for circumferential CAS using speckle-tracking method were determined in all patients. Intra-class correlation coefficients (95% confidence interval) were 0.98 (0.96 − 0.99) for intra-observer variability and 0.97 (0.93 − 0.98) for inter-observer variability, respectively. Bland-Altman plots also demonstrated low inter- and intra-observer variabilities; most data points fell within the limits of agreement with no evidence of fixed or proportional bias (Figure 3)

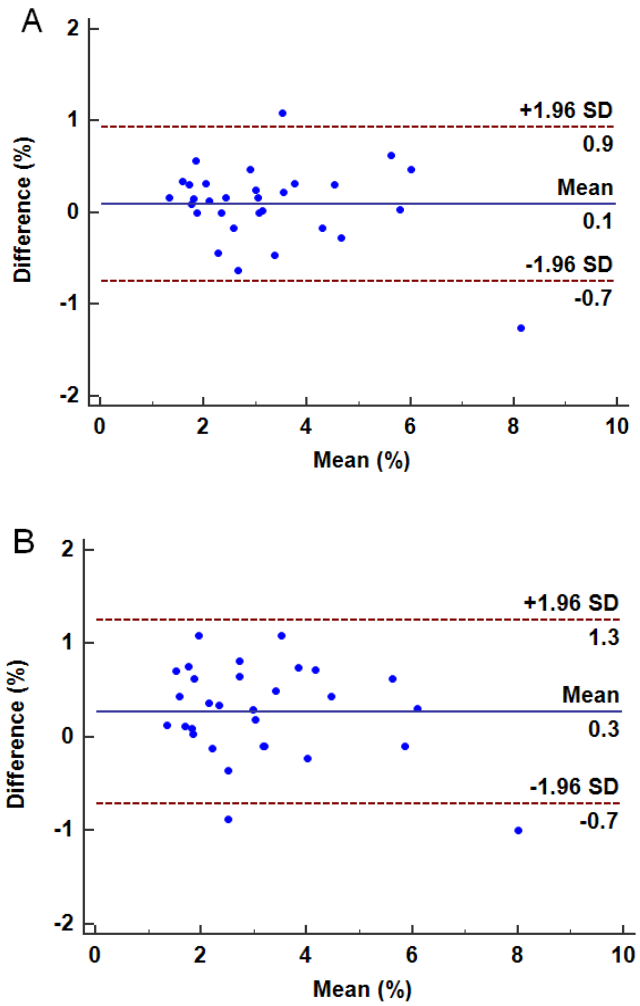

Figure 3. Bland-Altman analysis for circumferential CAS measurement

Bland-Altman plots of intra-observer (A) and inter-observer variabilities (B) for measurements of circumferential CAS by speckle-tracking method. The solid line is the mean difference between the 2 scans, while the limits of agreement are drawn as dashed lines (mean difference ± 2 SD). SD = standard deviation.

Discussion

The major findings of the current study are as follows; 1) short-term treatment with high-dose pitavastatin significantly improved carotid artery elasticity measured by speckle-tracking ultrasound, 2) the measurement of circumferential CAS by speckle-tracking imaging was feasible and reproducible. These findings suggest that high-dose statin treatment exerts beneficial effects on vascular and myocardial function beyond the lipid-lowering properties. This study also implies that speckle-tracking imaging-based measurements may allow the early assessment of pleiotropic effects of statins in patients with hypercholesterolemia.

This results are in line with previous observations and strengthen the idea that statin therapy may have beneficial effects on arterial stiffness.[5,6] Earlier basic research suggested biologically plausible mechanisms for the potential benefits of statin use on vascular function, including anti-inflammatory properties,[18] modulation of nitric oxide bioavailability,[19] and inhibition of LDL-C oxidation.[20] Several clinical studies proved that statin therapy can significantly improve vascular elasticity. In particular, many studies have focused on carotid arteries, since these are the most commonly used vascular beds for assessing early atherosclerosis in clinical practice. Specifically, a pilot study in statin-naïve subjects indicated that high-dose atorvastatin (80 mg daily) reduced carotid stiffness and increased distensibility.[5] Another study also showed that low-dose pitavastatin (1 or 2 mg daily) significantly improved the carotid artery elasticity in patients with

hypercholesterolemia.[6] Notably, these studies used classic arterial stiffness parameters from B-mode ultrasound to assess the effect of statin therapy. However, these parameters cannot directly measure the expansion of the intima-media wall, but rather the extension of the arterial wall according to the systolic and diastolic lumen diameter. For such reasons, conventional parameters have limited validity and reproducibility.[7] For example, their ability to detect age-dependent differences in carotid elastic properties was inferior to that of speckle-tracking-based strain analysis.[13] In the present study, after 3 months of high-dose pitavastatin treatment, there was a significant improvement in carotid strain assessed by both speckle-tracking-and conventional methods. However, when we measured stiffness index, the improvement in this BP-adjusted index was observed when assessed by speckle-tracking imaging but not by traditional one. In this respect, it can be inferred that speckle-tracking imaging provides more sensitive assessment of arterial elasticity than B-mode ultrasound. Furthermore, it is noteworthy that IMT, a structural measure of subclinical atherosclerosis, did not significantly change after pitavastatin treatment. This finding is consistent with previous studies that have suggested no effect of statins on IMT regression.[5,6] Considering that a longer observation period is generally needed to see the pharmacological effects on structural changes in atherosclerosis,[21] 3-month follow-up might be too short to assess the impact of statin on carotid IMT. Hence, the assessment of carotid artery elasticity with speckle-tracking imaging can be useful in evaluating early effects of medical intervention.

Among various types of statins, pitavastatin was used in the present study, which has a comparable lipid-lowering efficacy to atorvastatin and rosuvastatin.[22,23] Compared to other statins, pitavastatin has been reported to produce better metabolic profiles such as improved glucose metabolism[24] and triglyceride control,[25] which was also shown in our study. In this regard, it can be speculated that the beneficial effects of pitavastatin on arterial elasticity may be maintained over a longer period of time, compared to other statins with adverse metabolic profiles.[26] Furthermore, given the negative impact of adverse glucose metabolism on the incidence and prognosis of HF,[27] pitavastatin can be considered as the preferred statin among patients with HF or at risk for HF, because of its positive effects on glycemic control and insulin resistance.[28]

Study limitations

The present study has several limitations. First, the sample size was small and the study population was exclusively middle-aged and elderly Korean. Thus, the extrapolation of our data to other ethnic populations should be undertaken with caution. Second, there was no control group in this study, limiting our ability to adequately assess the effect of pitavastatin on study outcomes in comparison with other statins or placebo. Third, the stiffness parameters were calculated at a single site without plaque in the left common carotid artery, which could increase the variation in measurements of these parameters. However, intra-observer and inter-observer variabilities were minimal in this study. Furthermore, great care was taken to select the same level of the

common carotid artery at baseline and at follow-up. Finally, this was a short-term observational study, therefore further studies are required to determine the clinical significance of our findings.

Conclusion

Short-term treatment with high-dose pitavastatin can significantly improve carotid artery elasticity assessed by speckle-tracking methods. Our findings lend preliminary support to the potential use of speckle-tracking imaging as a noninvasive tool for early assessment of treatment effect on vascular function in patients taking statin therapy.

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국문 초록

서론 : 혈관 역학 평가를 위해 이차원적 반점 추적 영상 (speckle-tracking imaging) 이 이용될 수 있다. 본 연구의 목적은 단기간 pitavastatin 의 치료가 경동맥 탄성에 주는 영향을 반점 추적 영상 기법으로 분석하는 것이다.

방법: 본 연구는 고콜레스테롤혈증을 가진 30 명의 환자 (나이, 61.6 ± 7.6 세, 남성 26.7 %)를 대상으로 하였다. Pitavastatin (4mg / 일)의 치료 전과 치료 3 개월 후의 carotid artery strain (CAS)의 변화를 반점 추적 영상을 통하여 측정 하였다.

결과 : 3 개월의 pitavastatin 치료 후 CAS 는 기준선과 비교하여 유의하게 증가하였다 (2.73 ± 1.17 %에서 3.27 ± 1.53 %, p = 0.029). 기존의 경동맥 탄성 측정법 중 B-모드로 측정한 strain 은 pitavastatin 치료 후 유의하게 향상되었다. 하지만 경동맥 intimal-medial thickness (IMT)의 경우에는 pitavastatin 전과 후에 유의한 변화가 관찰되지 않았다 (0.73 ± 0.18 에서 0.71 ± 0.16 mm, $p = 0.913$).

결론: 고용량 pitavastatin 의 단기 치료는 반점 추적 영상을 통하여 분석한 경동맥 탄성을 향상시켰다. 이러한 반점 추적 영상은 고콜레스테롤혈증 환자에서 약물 치료의 초기 효과를 비침습적인 방법으로 평가하는 데 도움이 될 수 있겠다.

주요어: pitavastatin; 경동맥; 탄성; 반점 추적 영상

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