

Rapid Rise in Cardio-Ankle Vascular Index as a Predictor of Impending Cardiovascular Events -Smooth Muscle Cell Contraction Hypothesis for Plaque Rupture -

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Abstract: Predictive factors for vascular events have not been established. The vasculature of the atheroma is supplied by penetration of the vasa vasorum through the smooth muscle cell layer from the adventitia. Smooth muscle cell contraction induces compression of the vasa vasorum, resulting in ischemia in intimal atheromatous lesions. Cardio-ankle vascular index (CAVI) has become known as an index of arterial stiffness of the arterial tree from the origin of the aorta to the ankle. CAVI reflects the progress of arteriosclerosis, and a rapid rise in CAVI indicates arterial smooth muscle cell contraction. We hypothesized that rapidly increased arterial stiffness evaluated by CAVI may be a predictor of impending cardiovascular events.

Keywords: arterial stiffness, stress, plaque rupture, CAVI

Plain Language Summary

Smooth Muscle Cell Contraction Hypothesis for Plaque Rupture

1. The atheroma is supplied by the vasa vasorum penetrating through the smooth muscle cell layer from the adventitia.
2. A rapid increase in cardio-ankle vascular index (CAVI) is associated with arterial contraction and compression of the vasa vasorum.
3. Compression of the vasa vasorum results in ischemia in intimal atheromatous lesions, leading to plaque rupture.
4. This process is supported by the high incidences of cardiovascular events following natural disasters or individual mental shock.
5. We have experienced several interesting cases in our daily practice using CAVI. However, it is very difficult to prove this fact in a prospective observational study. We proposed the “Smooth muscle contraction hypothesis for plaque rupture”.

Introduction

Cardiovascular diseases are significant problems in developed and developing countries.¹ Diabetes mellitus, hypertension, dyslipidemia, obesity, and smoking have been established as risk factors for cardiovascular diseases.² However, worsening of these factors does not necessarily provoke cardiovascular events immediately. Several hypotheses such as the cholesterol theory,³ response to injury hypothesis,⁴ and the plaque rupture theory of vulnerable plaques^{5,6} have been posited to explain atheromatous lesion formation and plaque rupture. However, these hypotheses do not explain impending cardiovascular events. Cardio-ankle vascular index (CAVI) is an index of arterial stiffness of the arterial tree from the origin of the aorta to the ankle.^{7,8} The cardio-ankle vascular index is independent from blood pressure at

time of measurement.^{9,10} Furthermore, CAVI has been established as an index of atherosclerosis progression.^{11–13} In addition, CAVI reflects functional stiffness, which is affected by arterial smooth muscle cell contraction.^{9,14} We previously observed a rapid rise in CAVI by chance, after which several patients experienced vascular events.¹⁵ Many studies have reported cardiovascular events immediately following large earthquakes,^{16–19} catastrophic incidents,^{20,21} or exciting events.²²

Recently, pathological studies showed that atheromatous lesions are rich in the vasculature near the vasa vasorum.^{23–25} The network of the vasa vasorum runs through the medial smooth muscle cell (SMC) layer from the adventitia and supplies blood to intimal atheromatous lesions, where many inflammatory reactions occur in response to cytotoxic substances such as oxysterols or other degradation products from infiltrated LDL.²⁶ Increased CAVI is a product of contraction of medial SMC, resulting in compression of the vasa vasorum in the medial layer and ischemia in intimal atheromatous lesions, leading to necrosis and plaque rupture. In this study, we proposed the “Smooth muscle cell contraction hypothesis for plaque rupture.”²⁷

Acute Stress and Cerebro-Cardiovascular Events

Fear, anxiety, overwork, and overexcitement are associated with sudden cardiac events. Ventricular arrhythmias in patients with implantable cardioverter-defibrillator (ICD) increased after the World Trade Center attack on September 11, 2001 in New York.²⁰ Moreover, the frequency of ventricular arrhythmias requiring ICD treatment also increased in Florida immediately following the World Trade Center attack.²¹ During the 2006 FIFA World Cup in Germany, the incidence of acute coronary syndrome (ACS) in Germany increased. A German group reported that stress-induced ACS was associated with a profound increase in inflammatory and vasoconstrictive mediators.²²

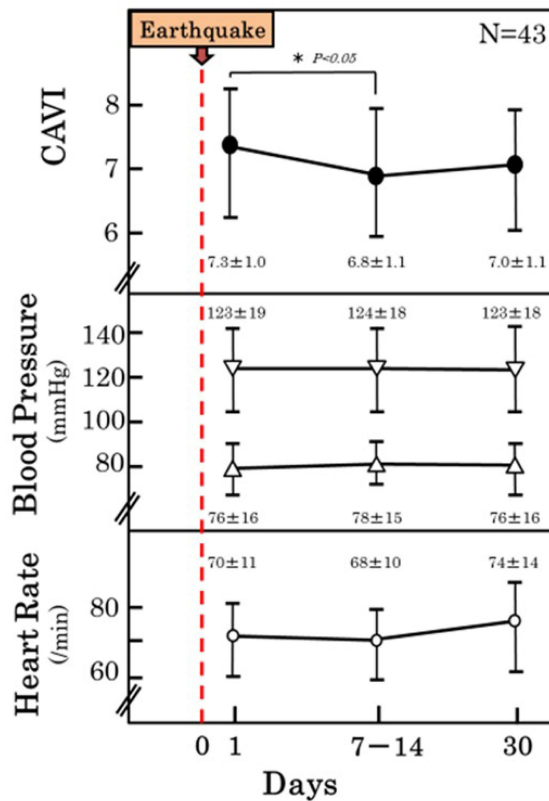
The Great East Japan Earthquake occurred in 2011. We measured CAVI of healthy individuals and patients with coronary artery disease in our hospital, which is located 300 km away from the epicenter. As shown in [Figure 1](#), the CAVI of healthy people decreased after 2 weeks, which indicated that CAVI had increased on the day of the earthquake. The CAVI of patients with coronary artery disease was elevated one week after the earthquake.¹⁵ Furthermore, there was a two-fold increase in patients who suffered from cerebral hemorrhage several days after the earthquake. The number of deaths in our town was higher in April of 2011 than that in 2009, 2010, or 2012 ([Figure 2](#)). We hypothesized that a rapid increase in CAVI might have been associated with increased mortality and morbidity.

We observed CAVI changes in several patients who suffered from myocardial infarction, cerebral hemorrhage, and aortic dissection. These cases showed a rapid rise in CAVI several weeks or months before the occurrence of vascular events. [Figure 3A](#) shows the case of an individual who suffered from an acute myocardial infarction 4 months after a rapid rise in CAVI. [Figure 3B](#) shows the case of an individual who suffered from a cerebral hemorrhage 7 days after a rapid rise in CAVI. [Figure 3C](#) is a case of an individual who suffered from aortic dissection 2 weeks after a rapid rise in CAVI. The CAVI in each case was measured periodically, and the rapid increase in CAVI was determined retrospectively to be associated with the cardiovascular events. The association between the high incidence of cardiovascular events and rapid CAVI increase after acute stress warranted further attention. Therefore, we aimed to further characterize this association.

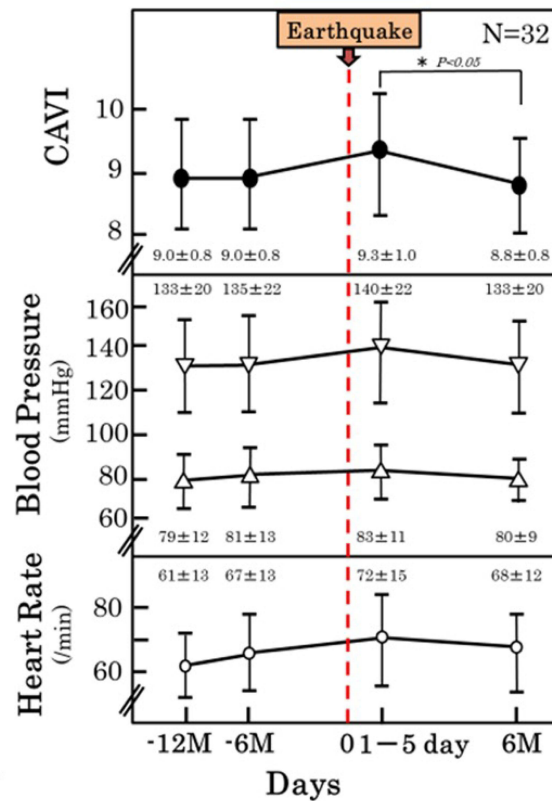
Rapid CAVI Increase

Cardio-ankle vascular index reflects arterial functional stiffness in addition to organic stiffness. Organic stiffness is high in atherosclerotic diseases and aging.²⁸ Organic stiffness is mainly affected by levels of collagen, elastin, hyaluronic acid, calcium deposition, and intimal smooth muscle cell proliferation. Functional stiffness has been shown to decrease in response to the $\alpha 1$ -adrenoceptor antagonist, doxazosin.⁹ Nitroglycerin administration also decreased CAVI in healthy individuals and individuals with atherosclerosis.¹⁴ Sakuma et al reported that administration of angiotensin II enhanced CAVI in rabbits.²⁹ These results suggested that CAVI reflects contraction or relaxation of arterial smooth muscle cells. These findings indicated that CAVI can be a measure of atherosclerotic state since organic stiffness and rapid changes in CAVI reflect functional stiffness and the state of smooth muscle

Healthy young adults



CAD patients

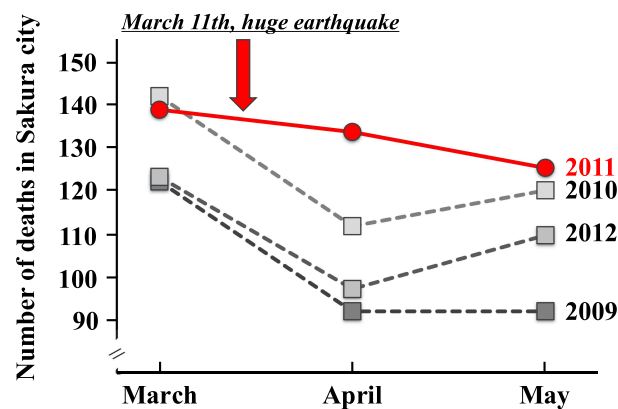


Data were expressed as mean ± SD.

Comparisons of each measurements were evaluated by Tukey–Kramer test.

Reference (15)

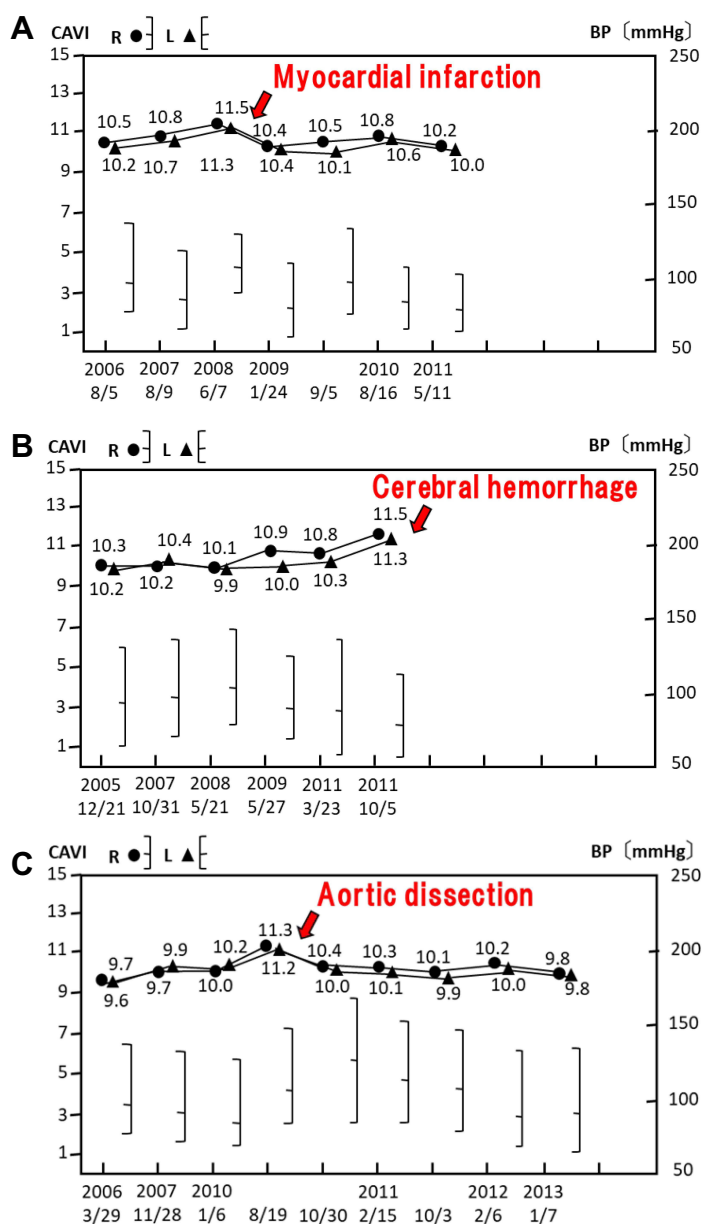
Figure 1 Changes in CAVI immediately following a large earthquake. Left: CAVI of a young healthy adult. Right: CAVI of patients with coronary artery disease. Reproduced from Shimizu K, Takahashi M, Shirai K. A huge earthquake hardened arterial stiffness monitored with cardio-ankle vascular index. *J Atheroscler Thromb*. 2013;20:503–511. Open Access.¹⁵



Reference (15)

Figure 2 Changes of number of fatalities in Sakura city around 2011. Reproduced from Shimizu K, Takahashi M, Shirai K. A huge earthquake hardened arterial stiffness monitored with cardio-ankle vascular index. *J Atheroscler Thromb*. 2013;20:503–511. Open Access.¹⁵

cell contraction. Furthermore, Nagasawa reported that blood removal decreased BP and pulse wave velocity (PWV), but increased CAVI. Blood transfusion returned all parameters to baseline.¹⁰ These findings indicated that CAVI, which is unaffected by blood pressure, is a better measure of arterial smooth muscle cell contraction.^{9,10}



Reference (27)

Figure 3 Cases of cerebro-cardiovascular events after a rapid increase in CAVI (A) a case of acute myocardial infarction. (B) A case of cerebral hemorrhage. (C) A case of aortic dissection. Reproduced with permission from Dove Medical Press. Shimizu K, Takahashi M, Sato S, et al. Rapid rise of cardio-ankle vascular index may be a trigger of cerebro-cardiovascular events: Proposal of smooth muscle cell contraction theory for plaque rupture. *Vasc Health Risk Manag.* 2021;17:37–47.²⁷

Microcirculation by the Vasa Vasorum in Atherosclerotic Lesions

Advanced intimal atheromatous lesions are rich in microvessels.^{23–25} The vasa vasorum penetrates the medial smooth muscle cell (SMCs) layer from the adventitia to the intimal layer. The medial SMCs of the arterial wall can contract or relax, even during arteriosclerosis, as evidenced by decreased CAVI in response to nitroglycerin administration in healthy individuals and individuals with atherosclerosis.¹⁴ Increased CAVI is characterized by vasoconstriction, which compresses the portion of the vasa vasorum that penetrates the medial layer, resulting in reduced blood flow to the atheromatous core in the intima.

Previously, nutrient supply to intimal atheromatous lesions was believed to be mediated by infiltration from blood vessel cavities through endothelial cell layers. To demonstrate that blood supply to intimal atheromatous lesions was delivered by the vasa vasorum from the adventitia, we evaluated the vasculature following carotid endarterectomy. As

shown in Figure 4, we performed a carotid endarterectomy in a patient 90% cervical artery stenosis caused by an atheromatous lesion. During the surgery, when the intimal atheromatous layer of the carotid artery was peeled off, the medial smooth muscle layer was removed. After peeling off the intimal layer, bleeding was immediately observed on the surface of the medial smooth muscle cell layer. However, when the surface of this medial smooth muscle layer was covered with gauze dipped in noradrenaline, the bleeding stopped. This finding indicated that the blood supply to the intimal atheromatous lesion was mediated by the vasa vasorum, and this blood flow was interrupted by contraction of medial SMCs. These observations strongly suggested that the vasa vasorum supplied blood from the adventitia to intimal atheromatous lesions.

Osada et al reported that most aortic dissections initially developed in the outer third of the media alongside the vasa vasorum. They suggested that dysfunction of the vasa vasorum might play a key role in prolonged ischemia or malnutrition of the aortic media, resulting in necrotic layer formation in the dissecting aneurysm.³⁰

Smooth Muscle Cell Contraction Hypothesis for Plaque Rupture

We generated a new hypothesis regarding the vascular events that lead to plaque rupture through ischemic damage and necrosis induced by a rapid rise in CAVI, as shown in Figure 5. The mechanism and process of plaque rupture as proposed by this hypothesis is as follows:

First Step

Exposure to cardiovascular risk factors and aging results in formation of atheromatous lesions. A lipid pool forms at the site via cholesterol deposition. The deposited cholesterol is oxidized in response to oxidative stress,³¹ resulting in

Atherosclerosis of the carotid artery and endarterectomy

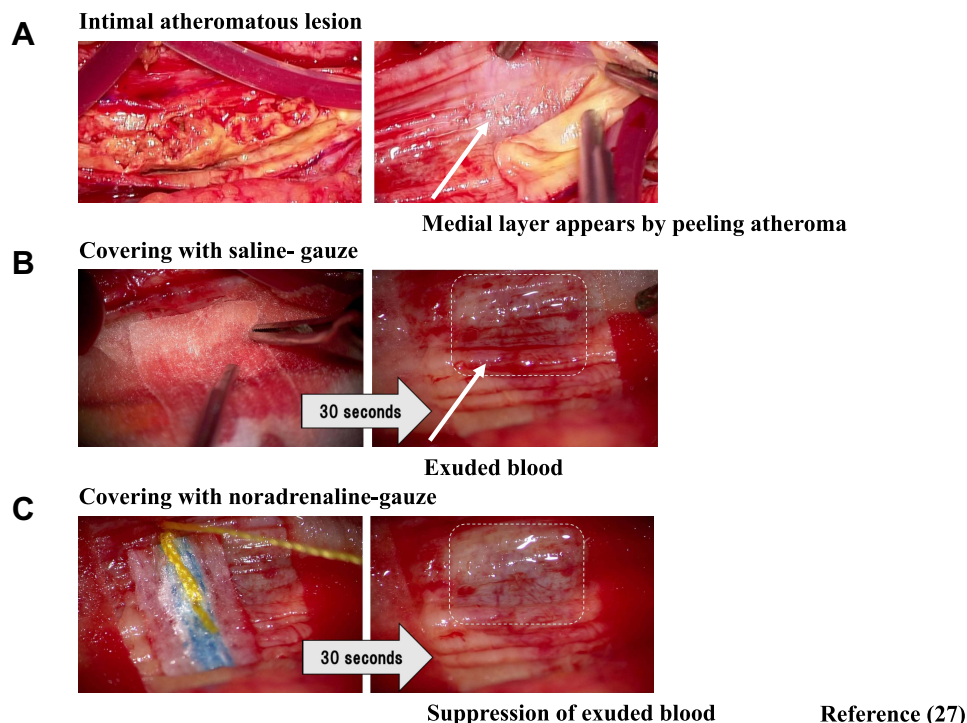


Figure 4 Bleeding on the surface of denuded medial smooth muscle layer during carotid endarterectomy. **(A)** Atheromatous lesion in the intima of the carotid artery (left) and denuded medial smooth muscle layer exposed by peeling off the intimal atheromatous layer during endarterectomy (right). The surface of medial smooth muscle cell layer was immediately covered with exuded blood. **(B)** When denuded medial smooth muscle layer was covered with gauze dipped with saline, the surface of medial smooth muscle layer continued to bleed. **(C)** When denuded medial smooth muscle layer was covered with gauze dipped with noradrenaline, the surface of medial smooth muscle layer stopped bleeding. These findings indicated that the vasa vasorum supplied blood from the adventitia to the intimal atheromatous lesion, and this blood supply was blocked by contraction of the medial smooth muscle cells. Reproduced with permission from Dove Medical Press. Shimizu K, Takahashi M, Sato S, et al. Rapid rise of cardio-ankle vascular index may be a trigger of cerebro-cardiovascular events: Proposal of smooth muscle cell contraction theory for plaque rupture. *Vasc Health Risk Manag*. 2021;17:37–47.²⁷

Arterial Smooth Muscle Cell Contraction Hypothesis for Plaque Rupture

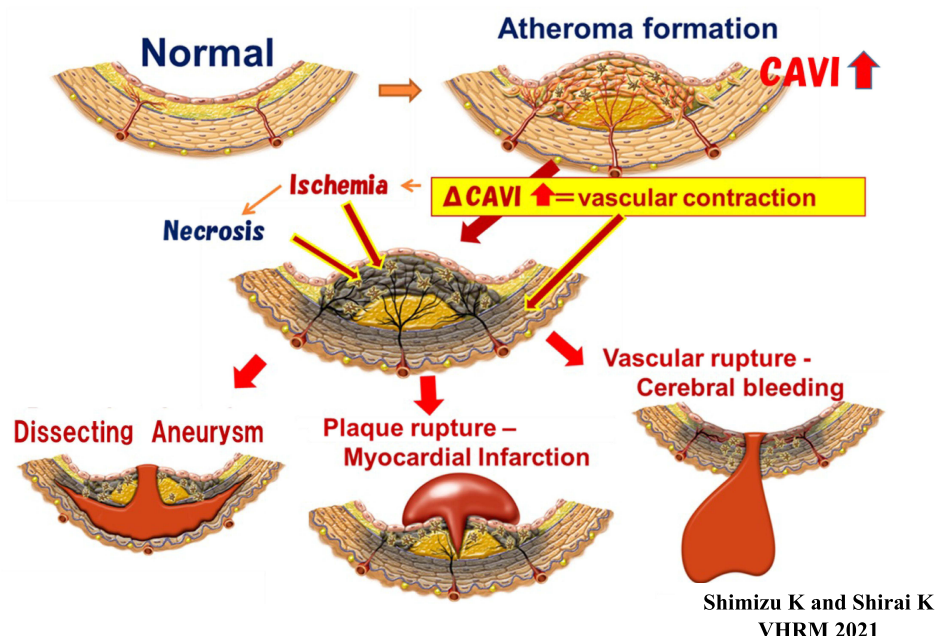


Figure 5 Smooth muscle cell contraction hypothesis for plaque rupture. Cardio-ankle vascular index increases gradually with atheroma formation. The vasa vasorum proliferates and penetrates the medial smooth muscle layer to supply blood to the intimal lesion. A rapid increase in CAVI results in contraction of the medial smooth muscle layer, leading to compression of the vasa vasorum and subsequent ischemia. A necrotic core forms and macrophages infiltrate the area and digest the necrotic core, resulting in plaque rupture. Dissecting aneurysm, plaque rupture-induced myocardial infarction, and vascular rupture-induced cerebral bleeding may then occur in the near future. Reproduced with permission from Dove Medical Press. Shimizu K, Takahashi M, Sato S, et al. Rapid rise of cardio-ankle vascular index may be a trigger of cerebro-cardiovascular events: Proposal of smooth muscle cell contraction theory for plaque rupture. *Vasc Health Risk Manag.* 2021;17:37–47.²⁷

oxidized cholesterol-induced apoptosis of SMC. In addition, oxidized cholesterol induced inflammation, which causes thickening of the intimal layer through proliferation of smooth muscle cells that migrate from the medial layer.³² These smooth muscle cells are the effectors of increased CAVI.

Second Step

Stresses such as fear, anxiety, overwork, or overexcitement promote arterial medial smooth muscle cell contraction via vasoconstrictive hormones such as catecholamines or inflammatory cytokines. This response results in increased CAVI.

Third Step

Contracted medial SMCs compress the micro vessels (vasa vasorum) penetrating through the medial layer (Figure 5). As a result, blood flow into the intimal atheromatous layer is interrupted, resulting in susceptibility of plaques to ischemia. This ischemia results in necrosis of the core of the intimal atheromatous lesion. Then, macrophages congregate around the necrotic core and begin to digest the necrotic tissue. The cap of the vulnerable plaque then becomes thin and ruptures.

In the coronary artery, plaque rupture causes thrombus formation on the surface of the intimal layer, leading to myocardial infarction. In the aorta, the necrotic core in the wall could develop into a dissecting aneurysm. In the cerebral artery, the thin arterial wall could be easily ruptured by necrosis of the SMC layer, resulting in brain hemorrhage.

When Should CAVI Be Measured in Patients with Atherosclerosis

Periodic measurement of CAVI might recommended in addition implementation of strategies to control various risk factors in patients with atherosclerosis. If a rapid rise in CAVI of 0.7–1.0 occurs, measures should be taken to relieve any stresses to decrease CAVI as quickly as possible. Coefficient variation (CV) of CAVI measurement was reported 3.8%.⁷ We thought that over two times of CV is supposed to be unordinary panic value. Then, we adopted + 0.7. In addition,

Otsuka et al revealed that $\Delta\text{CAVI} \geq 0.5$ during 6 months of observation period was associated with the high risk of CV event.³³ A rapid rise in CAVI of 0.7–1.0 is just tentative and might be changed in the future.

Conclusion

A rapid rise in CAVI in cases with high CAVI might be an important warning sign of impending cardiovascular events. We proposed the “Smooth muscle cell contraction hypothesis” for plaque rupture. Further studies are needed to evaluate this hypothesis.

Periodic measurement of CAVI might be recommended in addition to control of various risk factors. If a rapid rise of CAVI by 0.7–1.0 occurs, stresses should be relieved to decrease CAVI as quickly as possible.

Ethics

Everyone who participated in our past study gave written informed consent after receiving a detailed description of the procedures in accordance with the Declaration of Helsinki; the study was reviewed and approved by the Ethics Committee of Toho University (25045, Ref. 14) or Toho University Sakura Medical Center (2011-004, Ref. 15).

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest related to this work.

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