Journal of the American College of Cardiology Vol. 51, No. 6, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.10.030

Localized Elevation of Shear Stress Is Related to Coronary Plaque Rupture

A 3-Dimensional Intravascular Ultrasound Study With In-Vivo Color Mapping of Shear Stress Distribution

Yusaku Fukumoto, MD, Takafumi Hiro, MD, PHD, FACC, Takashi Fujii, MD, PHD, Genta Hashimoto, MD, Tatsuhiro Fujimura, MD, Jutaro Yamada, MD, PHD, Takayuki Okamura, MD, PHD, Masunori Matsuzaki, MD, PHD, FACC

Yamaguchi, Japan

Objectives The purpose of the present study was to assess the relationship between shear stress distribution and coronary plaque rupture by means of a new color-mapping program of shear stress with 3-dimensional intravascular ultrasound (IVUS).

Background Various in-vitro studies have demonstrated that shear stress of the vascular lumen is one of the important determinants of coronary plaque vulnerability. However, the in-vivo relationship between shear stress and plaque rupture is still unclear.

Methods In the present study, 3-dimensional IVUS was used to obtain spatial information on luminal geometry from 20 patients with acute coronary syndrome having a distinct ulcerative lesion. These 3-dimensional contours for each lumen were first reconstructed into mesh polygons, and then analyzed by means of a program for calculating the fluid dynamics. The flow was considered to be a constant laminar one. Then, colorized mappings of the distribution of the streamline, blood pressure, and shear stress were performed. The original luminal contour for each ruptured lesion was obtained by smoothing and extrapolation.

Results All patients had a coronary plaque rupture in the proximal or top portion of the plaque hill. In the color mapping, localized elevation of blood pressure and shear stress could be observed on each plaque surface. The shear stress concentration was frequently correlated with the plaque rupture site (kappa = 0.79).

Conclusions Although the absolute value of shear stress is not sufficient to directly provoke mechanical destruction of the fibrous cap, localized high shear stress might be a trigger of fibrous cap rupture. (J Am Coll Cardiol 2008;51: 645–50) © 2008 by the American College of Cardiology Foundation

Coronary plaque rupture with subsequent thrombus formation is the most important mechanism leading to acute coronary syndrome (ACS) (1–3). A plaque that is prone to rupture is denoted as vulnerable plaque. Such a plaque cluster is usually associated with eccentric noncalcified morphology (3,4), a thin fibrous cap (3,5–7), a large lipid core (3,5,6,8,9), infiltration of inflammatory cells (7,10), and spotty calcification (11). Coronary plaque rupture occurs frequently at the shoulder of eccentric plaques (8). It has been theoretically suggested that this portion is subjected to excessive concentration of circumferential tensile stress, which might provoke its catastrophic rupture (12). Abnormal accumulation of inflammatory cells can also be observed at this portion, and these accumulated cells secrete proteolytic enzymes or cytokines to weaken the plaque surface structure (13,14). However, it is still unclear which factor is mainly responsible for the outbreak of plaque rupture.

Shear stress is one of the important physical factors in the process of atherosclerosis. Shear stress is defined as a stress produced by blood flow, which tends to cause a vessel endothelium to slide or to be deformed. The value is calculated as blood viscosity multiplied by the first derivative of flow velocity with respect to the distance from the vessel wall. It

From the Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan. This work was partly supported by a grant-in-aid for scientific research of the Ministry of Education, Japan (grants 16590690 and 19590819), Health and Labour Sciences research grants: Comprehensive Research on Cardiovascular Diseases from Ministry of Health, Labour, and Welfare of Japan; and Knowledge Cluster Initiative of the Ministry of Education, Japan. This study was presented, in part, at the 54th Annual Scientific Sessions of the American College of Cardiology, Orlando, Florida, March 6–9, 2005. Drs. Fukumoto and Hiro contributed equally to this work.

Manuscript received March 7, 2007; revised manuscript received August 23, 2007, accepted October 11, 2007.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
BP = blood pressure
IVUS = intravascular ultrasound

has been recognized that the portions of arterial vessels that are subjected to low shear stress are those most likely to be associated with plaque formation and remodeling (15,16). Atherosclerotic plaques are frequently located in the outer side of the bifurcation at a flow divider and in the inner curvature of vessels (15,17,18), in which shear stress is relatively low. Some ex-vivo studies have demonstrated that high shear stress may be related to plaque rupture (19). Previous studies have described the complex spatial and temporal interactions between shear stress distribution and changes in vascular anatomy (20,21). However, in-vivo evidence of such a relation is limited.

Intravascular ultrasound (IVUS) provides 2-dimensional and even 3-dimensional high-quality tomographic images of coronary plaque and the vessel wall in vivo. Krams et al. (22) proposed a method of 3-dimensional color mapping of coronary shear stress along the vessel wall by using IVUS and coronary angiography. This method is a sophisticated but complicated technique that requires tremendous time to calculate shear stress. We, thus, developed a more simplified method for color mapping the distribution of shear stress, which is a user-friendly program with less calculation time that can be performed with a personal computer and some commercially available applications. The purpose of the present study was to assess the relationship between shear stress distribution and coronary plaque rupture by means of this new color-mapping program and 3-dimensional IVUS.

Methods

Acquisition of IVUS images. Twenty human ruptured coronary lesions selected from patients (15 men, 5 women; age 63 ± 7 years; range 54 to 74 years) diagnosed with ACS were imaged by IVUS (Atlantis SR pro, 2.8-F, 40-MHz, Boston Scientific Corporation/SCIMED, Maple Grove, Minnesota). These lesions were selected from proximal segments of the left anterior descending artery (n = 15) or the middle portions of the right coronary artery (n = 5). Vessel segments in which the IVUS catheter could be inserted as straight as possible (curvature radius of the IVUS catheter path >80 mm) were selected. This was ensured by angiograms that at least showed no significant bending at all throughout the observed portion of interest. The tortuous lesions in which the inserted IVUS catheter bent significantly, and the lesions associated with a significant mass of thrombus on the plaque surface, were excluded.

The transducer was withdrawn automatically using a motorized pullback device (pullback speed = 0.5 mm/s). Intravascular ultrasound images were all recorded on S-VHS videotape for off-line analysis. The images were then digitized and analyzed with commercially available software for longitudinal reconstructive IVUS image analysis (Netra IVUS, ScImage, Inc., Los Altos, California).

Ruptured plaque was defined as a lesion with a distinct cavity that communicated with the lumen accompanied by a residual fibrous cap fragment. Although the sensitivity or specificity of IVUS to identify areas of plaque rupture is not validated (American College of Cardiology/American Heart Association guidelines [23]), the plaques we selected had a distinct rupture site that was readily detected, and required the agreement of 2 independent experienced observers. The lesions observed were considered as the culprit lesion, which was compatible with the clinical findings. Ruptured plaques were divided equally into 3 longitudinal portions with longitudinal IVUS findings: a proximal, middle (corresponding to the highest point of the raised plaque), and distal portion (Fig. 1). The middle portion was defined as the plaque portion that had the thickest part of the plaque.

Color mapping of shear stress. The technique of color mapping was developed by modifying the method of Krams et al. (22). The 3-dimensional lumen geometry of the vessel obtained from IVUS was first applied to define a mesh polygon structure that was subsequently used for the analysis of computational fluid dynamics. The generation of the mesh polygon was performed in 2 steps. The lumen contour was traced along the longitudinal plane images of 3-dimensional IVUS, by referring to cross-sectional views. The same procedure was done by revolving the plane in increments of 10 degrees (a total of 36 longitudinal luminal contour images) (Fig. 2) around the axis to the centerline of the IVUS catheter. Since it was hard to image the whole contour of side branches with the IVUS catheter inserted through the main vessel, we just measured the diameter and the bifurcation angle of each side branch at the bifurcated portion. We then straightened the lumen of the side branch over at least 100 mm, which would not affect the shear stress calculation along the main vessel. At the ruptured portion, the tracing of the luminal edge of the residual fibrous cap

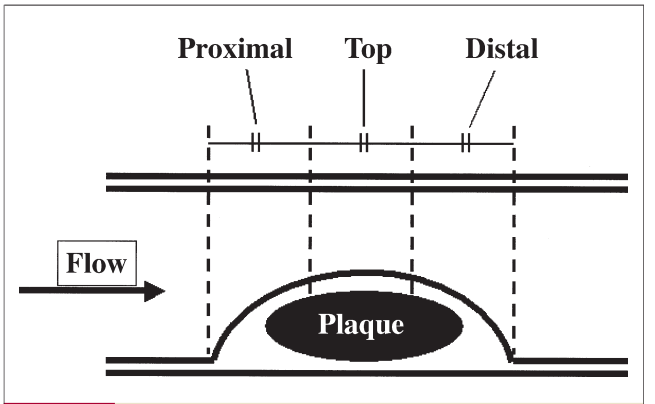

Figure 1 Classification of Plaque Rupture Sites

The plaque from the proximal shoulder to the distal shoulder was divided into 3 equal parts in the longitudinal direction.

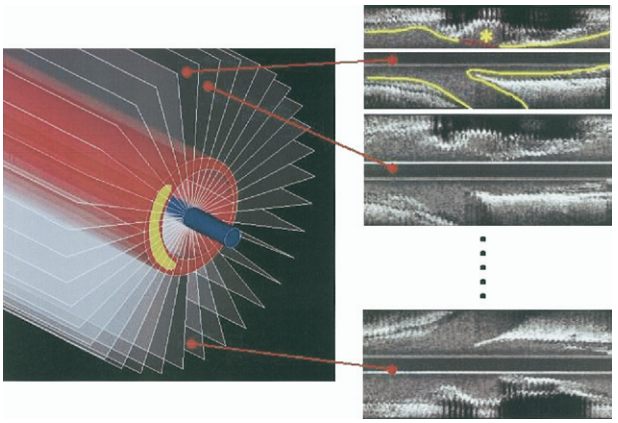

Figure 2 Reconstruction of the Coronary Lumen Contour

The lumen contours traced from a total of 18 longitudinal intravascular ultrasound images while revolving the plane in increments of 10° were used to reconstruct the whole profile of the coronary lumen. These data were exported into the program of shear stress calculation. At the rupture site, the contour was extrapolated at the orifice of the ulceration cavity **(*)**.

was smoothly extrapolated to reconstruct the luminal contour before the rupture. When the cap was too deformed to trace, the lesion was excluded. To assure that one can reasonably extrapolate the original contour of a plaque by connecting the dots between the edges of the craters, ruptured plaques with a significant amount of residual fibrous cap, which did not have unnatural cambers, were selected. The 3-dimensional luminal contour was then transferred to a commercially available program to create a mesh polygon structure (Pro-modeler 2003, CD-Adapco Japan, Kanagawa, Japan). The data were then used to conduct a computational stress analysis using the finite element model for the purpose of color mapping of the shear stress distribution along the plaque surface.

The computational fluid dynamics analysis was performed using a commercially available application (Star LT, CD-Adapco Japan) to calculate the distribution of the velocity and the directional vector of the blood stream inside the lumen, the blood pressure (BP), and the shear stress on the plaque surface. The shear stress at the lumen surface of the artery was calculated as the product of viscosity and the gradient of blood velocity at the wall. A color mapping of the shear stress distribution was then performed. The spatial resolution of the subunits was approximately 0.01 mm^2. The structure was automatically meshed with 4-noded trilateral plane-strain elements. In this calculation, several assumptions were made as follows: 1) the flow was a constant laminar one; 2) there was a uniform stationary inflow velocity of 30 cm/s at the entrance of the vessel; 3) there was no flow resistance at the outlet; 4) there was no flow "slip" on the vessel wall. The detailed intravascular flow characteristics were obtained by solving the transport equations governing the conservation of mass and momentum (24). We also assumed that the arterial wall was solid and that the blood was incompressible, homogeneous, and Newtonian (25) with a density of 1,050 kg/m^3 and a viscosity of 0.003 PaS (26). It is said that a uniform inflow condition influences the shear stress distribution at least for 2 diameter lengths downstream and could thus also influence the shear stress distribution at the plaque side. The plaques analyzed were located at least 3 diameter lengths far away from the inflow entrance. When there is a flow divider in the vessel observed, the flow towards each branch was prorated according to the value of the inlet cross-sectional area (27).

This study was approved by the Institutional Review Board of the Hospital of Yamaguchi University School of Medicine (H18-11).

Statistical analysis. Values were expressed as the mean ± standard deviation. The location of the focal elevation of shear stress and the ruptured portion were classified into the proximal, the middle, and the distal portions along the longitudinal plaque surface. The kappa statistics method was used to assess the measure of agreement in this classification between the location of rupture and the location of the focal elevation of shear stress or pressure. This method does not require any assumption that there is a correct diagnosis. The value of kappa ranges from −1.0 to +1.0. A value of 0 indicates chance agreement, whereas a value of +1.0 shows perfect agreement. A negative value indicates that disagreement is predominant among observers. A value >0.75 implies excellent agreement, values from 0.40 through 0.75 suggest fair-to-good agreement, and values less than 0.4 imply poor agreement (28).

Results

Among the 20 patients selected, 15 had acute myocardial infarction and 5 had unstable angina. No cases had previous ACS or any coronary intervention. The mean percentage of stenosis at the atherosclerotic plaque of interest was 67.6 ± 18.0% by angiography. The mean percentage of stenotic area at the ruptured site and the maximum percentages of stenosis around the plaque in IVUS were 70.0 ± 8.4% and 79.7 ± 7.4%, respectively.

Characteristic IVUS profile of ruptured plaque. The echo-intensity of ruptured plaques was generally low (n = 19 of 20: 95%). The calcification was observed near but not directly adjacent to the ulcerative plaque cavity (n = 17 of 20: 85%). Deep calcification was frequently observed (n = 15 of 20: 75%), whereas superficial calcification around the rupture site was detected only in 3 cases. Intravascular ultrasound revealed that 13 plaques were ruptured at the proximal portion, and 7 were ruptured at the top or middle portions. No rupture occurred at the distal portion of the plaque.

BP and shear stress distribution. The calculated blood wall pressure was 82 ± 18 mm Hg. In the color mapping, several specific areas that had a localized elevation of shear stress or BP were clearly revealed. The localized elevation of

shear stress or BP was defined as a clearly visualized and localized spotty elevation of shear stress. The highest value of shear stress divided by the lowest one within the whole plaque surface was more than 7.4 in all subjects.

Representative examples are shown in Figure 3 and 4. The BP was elevated focally at the proximal portions in only 2 plaques (10%), and was not elevated in any specific area in 18 plaques (90%), although an overall longitudinal gradation of the pressure was observed along the vessel wall. In these cases, the BP was uniformly or smoothly distributed without any clearly visualized focal elevation. However, the shear stress was focally elevated at the proximal portions in 12 plaques (60%), at the middle portions in 8 plaques (40%), and not at all at the distal portions. The focal elevation of shear stress was significantly matched with the rupture location (kappa = 0.79).

Discussion

In the present study, a color mapping of the shear stress by use of a simplified computational analysis from 3-dimensional IVUS plaque images revealed that a localized elevation of shear stress on the plaque surface was related to coronary plaque rupture. This is the first in-vivo documentation visually demonstrating a relationship between shear stress distribution and the location of plaque rupture. Although the calculation of shear stress in this study used a number of assumptions, our findings suggest that this method of color mapping the shear stress along the plaque surface might be a useful tool for predicting plaque rupture sites.

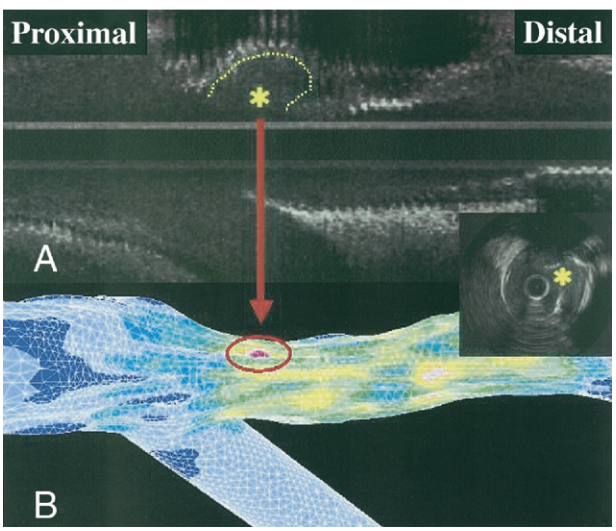

Figure 3 **Representative Case 1: The LAD of a 60-Year-Old Man With UA**

(A) The longitudinal intravascular ultrasound image. Plaque rupture was observed at the proximal site of the plaque. **(B)** Color mapping of the shear stress distribution. A localized elevation of shear stress was observed on the plaque surface **(circle)**. This portion corresponded to the rupture site **(*)**. LAD = left anterior descending coronary artery; UA = unstable angina.

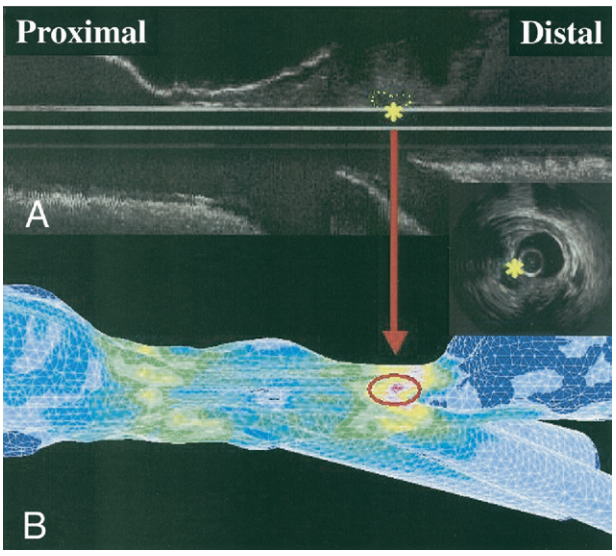

Figure 4 **Representative Case 2: The LAD of a 57-Year-Old Man With AMI**

(A) The longitudinal intravascular ultrasound image. Plaque rupture was observed at the proximal site of the plaque. **(B)** A focal elevation of shear stress was observed on the plaque surface **(circle)**. This portion corresponded to the rupture site **(*)**. AMI = acute myocardial infarction; LAD = left anterior descending coronary artery.

Plaque rupture and shear stress. It is generally thought that a specific cluster of plaques, referred to as vulnerable plaques, is likely to exist, and numerous efforts in plaque imaging are now being concentrated on how to accurately predict the location of plaque rupture. It has been shown in pathological studies that plaque rupture frequently occurs in a noncalcified eccentric atherosclerotic plaque with nonsevere stenosis (3,4), expansive remodeling (29,30), a thin fibrous cap (3,5–7), a large lipid core (3,5,6,8,9), macrophage infiltration (7,10), spotty calcifications (11), and lack of a massive superficial calcification (31,32). However, such plaques can usually be observed at multiple nonculprit sites in the same patient with ACS (33,34). Therefore, there might be more specific triggering factors that finally provoke the plaque rupture at a particular site.

Previous studies have suggested that an excessive concentration of tensile stress within plaque may be one of the triggers of plaque rupture. When the tensile stress becomes greater than the fragility of the plaque surface, a catastrophic process of plaque rupture may be initiated. The tensile stress is increased by development of a lipid core, thinning of the fibrous cap, augmentation of plaque eccentricity (3–10, 29,30), and positive remodeling (31), whereas the fragility of plaque is aggravated by infiltration of inflammatory cells that secrete various proteinases and cytokines (13,14). In previous studies, shear stress was not considered as an important initiator of plaque rupture, because the absolute value of shear stress is negligibly low compared with the tensile stress. Therefore, the direct relationship between

shear stress and plaque rupture had not been extensively investigated, although there have been a number of studies assessing the effect of shear stress on plaque formation, or on the progression of plaque vulnerability (15,16). It is possible that the process of promoting the progression of atherosclerosis is quite different from that of initiating plaque rupture.

Shear stress is calculated as blood viscosity multiplied by the first derivative of flow velocity with respect to the distance from the vessel wall. Since the blood viscosity cannot be readily changed throughout a conduit vessel, the flow velocity gradient along the cross-sectional lumen diameter is an important factor to determine the value of the shear stress. When there is a prominent plaque hill inside a vessel lumen, the gradient is theoretically higher along the proximal part of the hill than along the distal one. Previous studies have demonstrated that plaque rupture is frequently observed at the proximal plaque portion (19), which was also shown in our study. Although spatial colocalization is not evidence of causality, our in-vivo results might support the idea that the plaque portion with high shear stress is prone to rupture.

Another interpretation suggested by our results is that "a localized elevation" of shear stress might be related to plaque rupture. A planimetric study of the macrophage contents in carotid plaques showed that macrophage-rich areas are more likely to be formed in the upstream shoulder than in the downstream shoulder of the same atherosclerotic lesion (19). Further, a previous in-vitro study by Gertz et al. (9) found that the calculated hemodynamic wall shear stress at the site of arterial narrowing was sufficiently strong to cause marked endothelial damage followed by platelet deposition and thrombus formation on exposed subendothelial tissues. Therefore, our study suggests that an elevation of shear stress in a limited area yields a significant heterogeneity in such endothelial damage, which, in turn, provokes a spiral catastrophic cascade leading to plaque rupture. Recently, Slager et al. (35) published a systematic review of the role of high shear stress as a key biological factor in provoking plaque destabilization. It has been proposed that high shear stress might stimulate endothelial cells to produce plasmin, nitric oxide, and transforming growth factor-beta, which are related to the degradation of proteoglycan matrix and/or the suppression of matrix production by smooth-muscle cells.

Clinical implications. A variety of factors may play a role in the initiation of plaque rupture, including tensile stress (31), turbulent pressure fluctuations (36), transient compression (37), sudden increase in intraluminal pressure (38), rupture of the vaso vasorum (39), material fatigue (3,8), and cellular inflammatory reactions (3,10). This study suggests that assessment of the shear stress within a plaque along the longitudinal axis of a vessel is also important for identifying vulnerable plaques. This approach may help identify vulnerable plaques or even help predict the point of future rupture.

Study limitations. In this study, in order to calculate the shear stress as accurately as possible, we chose relatively straight coronary segments of the lumen into which the IVUS catheter could be inserted with minimal bending. However, the use of 3-dimensional IVUS images still has the potential for errors in reconstructing the lumen contour. This study was performed under the assumption that the catheter path was almost straight (curvature radius of the IVUS catheter path >80 mm). This value of 80 mm was selected based upon a validation study, which assured that the real point of shear stress concentration would not be significantly deviated from the point obtained under the assumption that the catheter path was straight.

In this study, the electrocardiogram triggering was not applied to the cross sections before image segmentation. However, the pulsatile change in vessel diameter was $<5\%$, the effect of which might be neglected in the shear stress calculation. This study assumed that the presence of the catheter in the vessel did not alter the lumen morphology significantly.

Furthermore, the flow was considered to be laminar and Newtonian at the entry of the vessel conduit, and turbulent flow was not considered, while in-vivo coronary flow is pulsatile. This might have led to errors in calculating the shear stress. However, the most important finding is not the absolute value of the shear stress, but the distribution of the shear stress along the plaque surface. When the blood flow is turbulent, the location of the elevation of shear stress might also be changed, although the imaged plaque shape was not sufficiently tortuous to generate a turbulent flow in this study.

Another implicit assumption here is that the ruptured plaque has the same contour as the plaque before rupture. However, it should be stressed that our simplified method of shear stress color mapping could predict the location of the plaque rupture. Given the major set of simplifying assumptions as mentioned in the previous text, it is remarkable that such a high correlation between predicted and actual rupture locations was seen.

The included lesions were relatively stenotic (67% by angiography). It is well known that plaques prone to rupture are usually less stenotic. However, this study was regarding the concentration of shear stress rather than its absolute value. Therefore, if the similar concentration of shear stress can be observed even on less stenotic plaque surface, it might be extrapolated to say that such portion would provoke the plaque rupture.

Conclusions

A color mapping of the distribution of shear stress revealed that a localized elevation of shear stress could be observed on each plaque surface, and that the location of focally elevated shear stress was frequently matched with the plaque rupture site. This in-vivo study was the first to suggest that a localized elevation of shear stress might be related to coronary plaque rupture. Furthermore, the imaging of shear stress by our method may help identify vulnerable plaques or even help predict the sites of future rupture.

Reprint requests and correspondence: Dr. Takafumi Hiro, Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami Kogushi, Ube, Yamaguchi, 755-8505, Japan. E-mail: thiro@yamaguchi-u.ac.jp.

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