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Physiopathology of the Acute Coronary Syndromes

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1. Introduction

The widespread application of catheter-based interventions, and chronic treatment have contributed to improved long-term prognosis in patients with acute ST-elevation myocardial infarction (STEMI) [1-5]. Despite these indisputable achievements, a large number of individuals remain at substantial risk of severe first attack, recurrent disease and death. Patients with unstable angina were classified into three groups according to short-term risk of death or nonfatal myocardial infarction[6], and the results of noninvasive tests and the corresponding approximate mortality rates were reported [7].

Disruption, fissure, or erosion of an atherosclerotic plaque, with residual mural thrombus (RMT) has a fundamental role in the pathogenesis of acute coronary syndromes (ACS) [8-12]. Most of occlusive thrombi had a layered structure indicating an episodic growth by repeated mural deposits [13, 14]. Morphological studies indicated that plaque complications remained clinically silent days or weeks before the fatal event [15-18]. A RMT predisposes patients to recurrent thrombotic vessel occlusion [15, 16, 17], and plaque disruption, fissure or erosion with thrombus contributes to plaque development and progression [18]. Therefore, a marker that predicts disrupted, fissured or eroded plaque and the coronary thrombus may have practical clinical applications. The diagnosis of these lesions has been tried by several methods [19]. However, plaque disruption itself is asymptomatic, and the associated RMT is usually clinically silent [20]. To the best of our knowledge, markers as a sign of a disrupted, fissured or eroded plaque and a coronary thrombus are not available.

Scavenger receptor-mediated endocytosis of oxidized low-density lipoprotein by macrophages has been implicated in the pathogenesis of atherosclerosis. The differentiation of scavenger receptor A negative (SRA^-) monocytes in peripheral blood (PB) into SRA positive (SRA^+) macrophages was believed to take place in atherosclerotic lesions by stimulation of macrophage-colony stimulating factor (M-CSF) [21-24], and it was reported that freshly isolated blood monocytes were negative for SRA [25]. We surmised that plaque content might be exposed to the blood stream after disruption of plaque, and SRA^- monocytes might differentiate into SRA^+ cells in PB by stimulation of M-CSF contained in plaque content, and that increased SRA^+ cells in PB might be a useful indication of disrupted, fissured or eroded plaque and coronary thrombus.

Although several scavenger receptors, such as SRA, CD36, scavenger receptor-B1, CD68 and Lox-1 have been shown to bind oxidized low-density lipoprotein, SRA and CD36 are responsible for the preponderance of modified low-density lipoprotein uptake in macrophages [26]. In our study, we evaluated the utility of SRA, since SRA antigen is restrictedly expressed on macrophages [26], but CD36 is expressed not only on macrophages and monocytes but also on B lymphocytes.

We reported that the SRA index〔number of SRA^+ cells in 10 high power fields (HPF, ×400) of peripheral blood (PB) smear, upper limit: <30〕greater than 30 was considered to be a useful indication of disrupted, fissured or eroded plaque and coronary thrombus [27, 28]. In this paper, we described the composition of occlusive coronary thrombi obtained from patients with acute ST-elevation myocardial infarction (STEMI), the relationship between the SRA index and these thrombi, and the utility of SRA index as an indication of disrupted, fissured or eroded plaque and coronary thrombus in patients with ACS.

2. Study subjects

Eight autopsy cases with acute myocardial infarction, 393 patients with STEMI and 79 patients with unstable angina (UA) were examined. Patients with STEMI were treated with percutaneous intracoronary thrombectomy during primary angioplasty. High-sensitivity C-reactive protein (h-CRP), creatine kinase (CK) and creatine kinase-MB isozyme (CK-MB) were examined in patients with STEMI. PB from 43 apparently healthy men and women in their 20s was examined as a control.

3. Thrombectomy procedure

On admission, all patients were treated with 162 mg aspirin (Ebis, Osaka, Japan), and they underwent percutaneous coronary intervention of the infarct-related artery through the femoral access route with a 6F guiding catheter. Thrombectomy was performed with a Rescue™ catheter (Boston Scientific, Natick, MA, USA) or a TVAC catheter (NIPRO, Osaka, Japan). Aspirated blood and intracoronary material were collected in a collection bottle, which was equipped with a filter. Stent implantation was performed in 386 patients and all patients were treated with antithrombotic therapy.

4. Tissue processing and histopathological methods

Autopsy was performed 2 or 3 hours after death. Thrombi and organs were fixed in 10 % neutral formalin and embedded in paraffin, and examined using hematoxylin and eosin, and phosphotungstic acid hematoxylin (PTAH) sections. Papanicolaou-stained smears and paraffin-embedded sections were used for the immunohistochemical and immunocytochemical examination, which was performed with the simple stain MAX-PO method (NICHIREI Co., Tokyo, Japan) and with diaminobenzidine as the chromogen using mouse monoclonal anti-human glycoprotein 1b (CD42b, a platelet marker, 1:100; Novo Castra, Newcastle upon Tyne, UK), and mouse monoclonal anti-human SRA (CD204, a macrophage SRA marker, 1:200; Trans Genic Inc., Kumamoto, Japan) antibodies. An antigen retrieval method using citrate buffer and microwave heating was employed. As a negative control, the primary antibody was substituted by phosphate-buffered saline, and a positive stain was not observed in these controls.

5. Cytological methods

I believe that the method of cytological examination of peripheral blood is my original method [29]. Briefly, red blood cells were lysed with lysing reagent (826 mg of NH_4CL + 3.7 mg of EDTA-4Na + 100 mg of $KHCO_3$ in 100 ml H_2O), then nucleated cells were suspended in isotonic sodium chloride solution, and the suspensions containing about $5x10^6$ nucleated cells were smeared on glass slides using Auto smear CF-12 (Sakura Seiki, Tokyo, Japan). Cells that did not adhere to the glass slides were gently washed away with 95% ethanol solution. Smear preparations were fixed in 95% ethanol solution and stained with the Papanicolaou method. A smear preparation of PB is shown in figure 1. About one million and two hundred thousand nucleated cells were smeared in one slide. Nucleated cells are smeared evenly and precise nuclear structures are excellently preserved. About one thousand nucleated cells were observed in one high power field (x400, Figure 2).

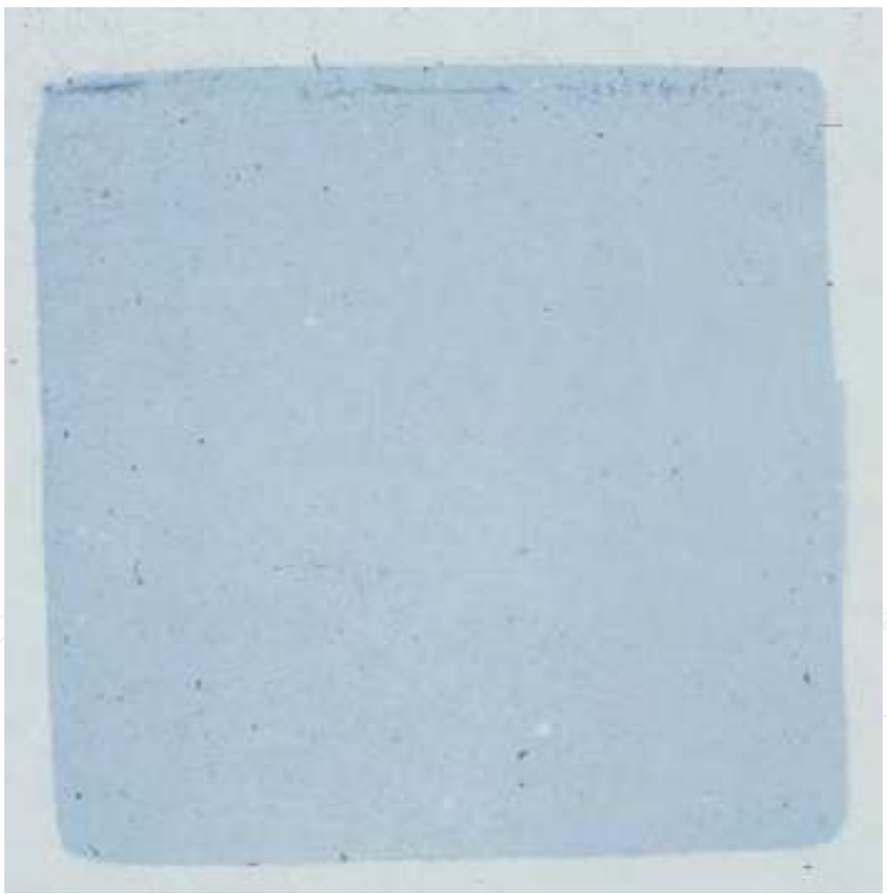

Fig. 1. A cytological preparation of peripheral blood stained with the Papanicolaou method. About one million and two hundred thousand nucleated cells are smeared in one slide. Papanicolaou stain.

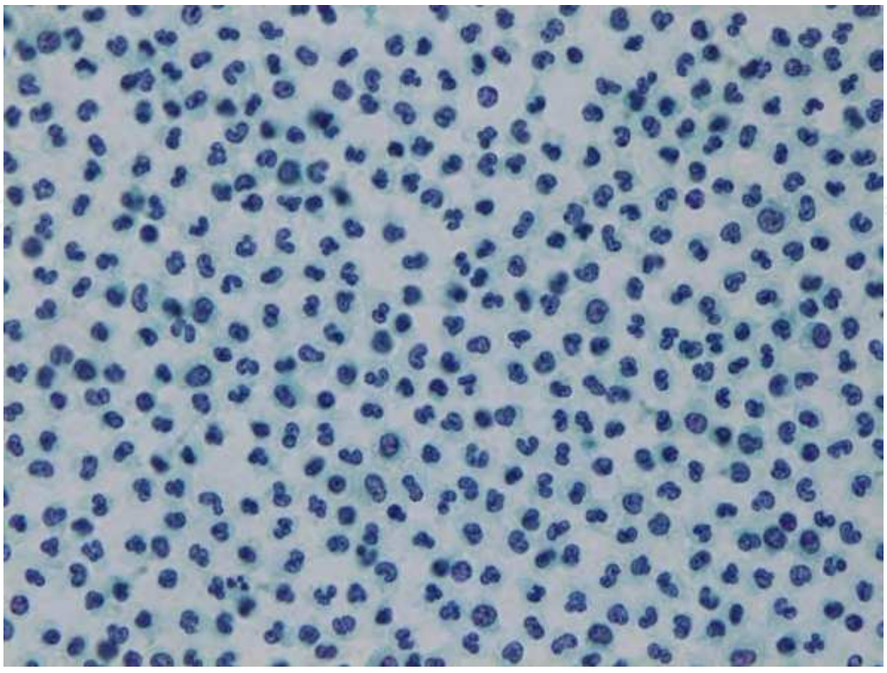

Fig. 2. About one thousand nucleated cells are observed in one high power field (×400). Nucleated cells are smeared evenly and precise nuclear structures are excellently preserved. Papanicolaou stain.

6. Definitions

Thrombi were classified into 4 groups according to previously published definitions considering age and constituents of thrombus[13, 30] : 1) an eosinophilic mass with neovascularization (organizing thrombus: OT), 2) a structureless eosinophilic (hyalin) mass (fibrin-rich thrombus: FT), 3) Thrombus containing significant quantities of platelets, erythrocytes, fibrin and leukocytes (mixed thrombus: MT), and 4) tightly packed but individually discernible platelets (platelet thrombus: PT). In this paper, we defined MT and FT as RMT. Plaque components were identified based on the presence of foamy macrophages, cholesterol crystals, collagen tissue, and/or calcification. Since the aspirated material was fragmented, and PT seemed to be the freshest thrombus, contact between PT and other types of thrombus (PT and MT: P-M, PT and FT: P-F,) and contact between PT and plaque content (P-C) were examined in all cases to investigate the process of coronary occlusion. Cases were classified into 3 groups according to the composition of the thrombus: group A, containing PT only and P-C; B, a MT only, P-M and P-C+P-M; C, P-F, P-M+P-F, P-C+P-F, and P-C+P-M+P-F. SRA^+ cells in PB that had the same size and nuclear shape as blood monocytes were defined as SRA^+ cells. The SRA index was defined as the number of SRA^+ cells in 10 HPFs of PB smear samples. Based on the SRA index of apparently healthy people in their 20s, we temporarily set the normal upper limit of the SRA index at 30 [27].

7. Autopsy cases

P-C was observed in 4 autopsy cases, P-M in 3 and P-M + P-F in 1. Numerous emboli of PT were observed in peripheral small arteries and capillaries of the infarct-related artery in 6 cases. SRA index exceeded 30 in 5 cases. A typical case with acute myocardial infarction is presented in figure 3 to 7. This patient is a forty-three year old male. He died suddenly. Postmortem examination revealed disruption of the plaque and occlusive thrombus in the left anterior descending artery (Figure 3). Thrombus is composed of platelet thrombus and mixed thrombus + fibrin-rich thrombus (Figure 4 and 5). Platelet thrombus was adhered on the inner side of mixed thrombus + fibrin-rich thrombus (Figure 4). Immunohistochemistry for CD 42b revealed that platelet thrombus was deeply stained than mixed thrombus + fibrin-rich thrombus (Figure 4). Fibrin mesh is contained in mixed thrombus + fibrin-rich thrombus but not in platelet thrombus (figure 5). SRA^+ cells are infiltrated in mixed thrombus + fibrin-rich thrombus but not in platelet thrombus (Figure 6). Numerous emboli of fragments of platelet thrombi were observed in small arteries and capillaries at the distal portion of the left anterior descending artery (Figure 7).

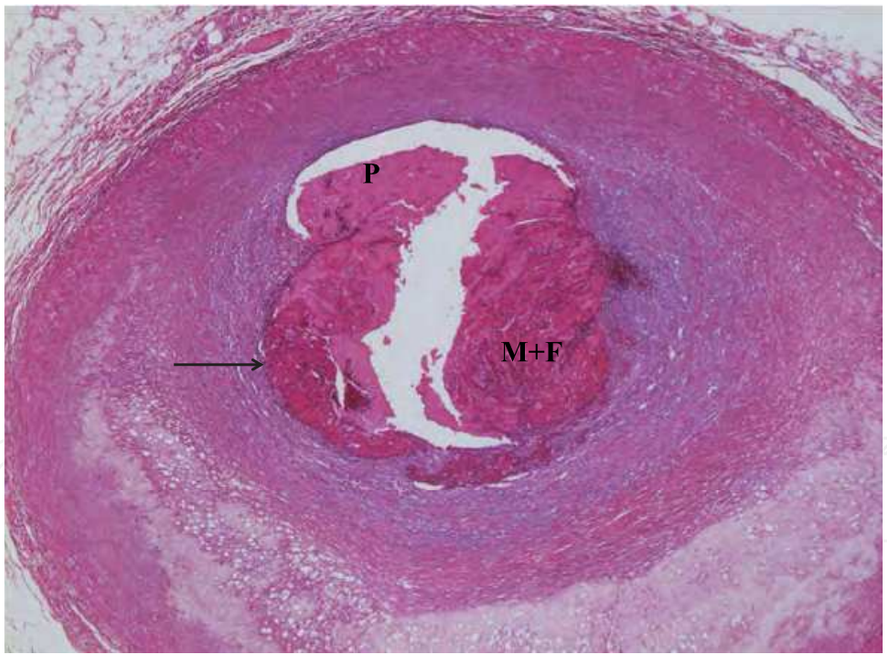

Fig. 3. Plaque disruption (arrow) and thrombus formation in the left anterior descending artery of the patients who died suddenly. Thrombus is composed of platelet thrombus (P) and mixed thrombus + fibrin-rich thrombus (P+M). hematoxylin and eosin.

Fig. 4. Serial section of figure 1. Platelet thrombus is deeply stained than mixed thrombus + fibrin-rich thrombus, and adhered on the inner side of mixed thrombus + fibrin-rich thrombus. Immunochemistry for CD42b.

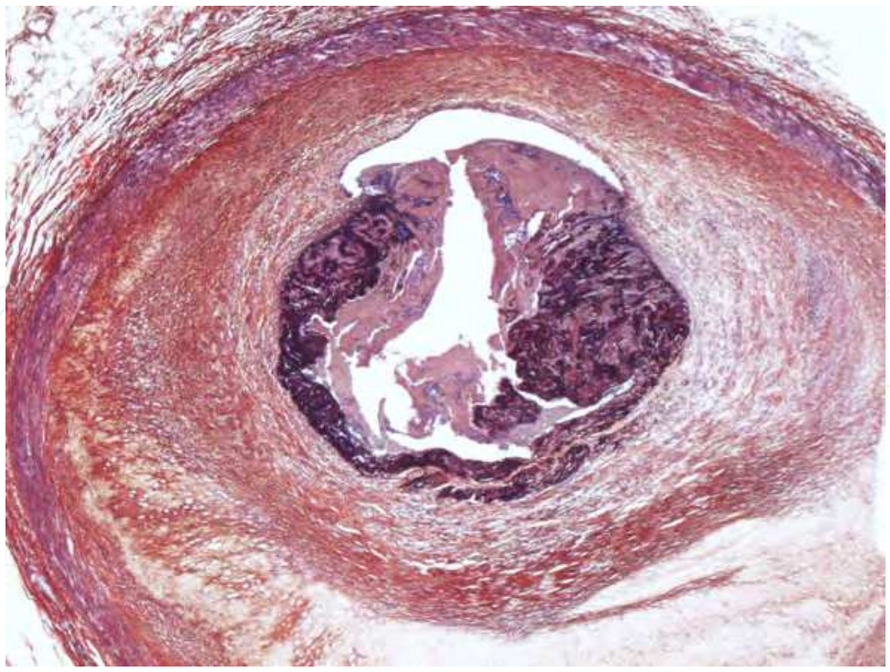

Fig. 5. Serial section of figure 1. Fibrin mesh is contained in mixed thrombus + fibrin-rich thrombus but not in platelet thrombus . phosphotungstic acid hematoxylin stain.

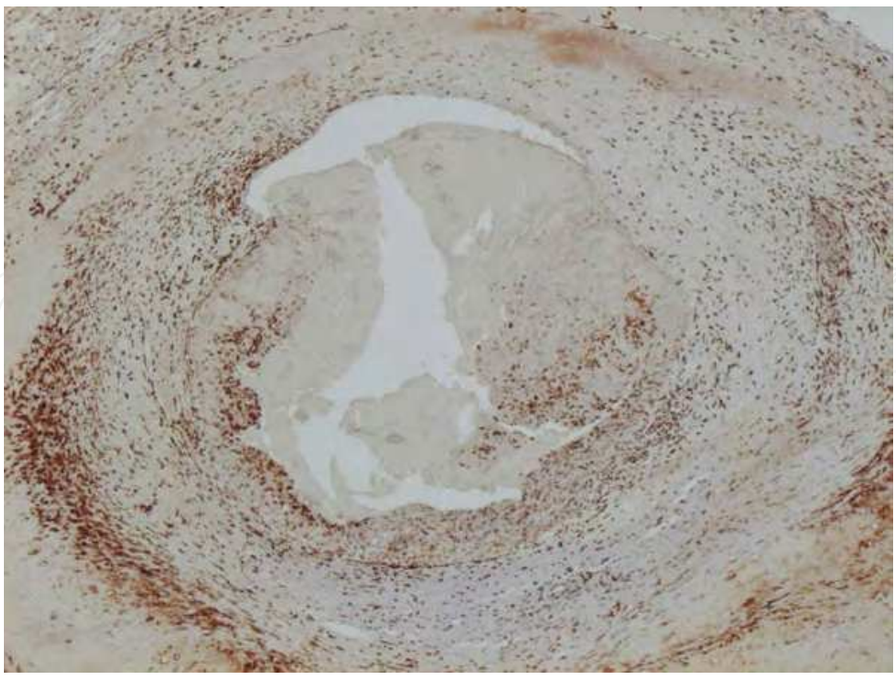

Fig. 6. Serial section of figure 1. Scavenger receptor A positive cells are infiltrated in mixed thrombus + fibrin-rich thrombus but not in platelet thrombus. Immunochemistry for scavenger receptor A.

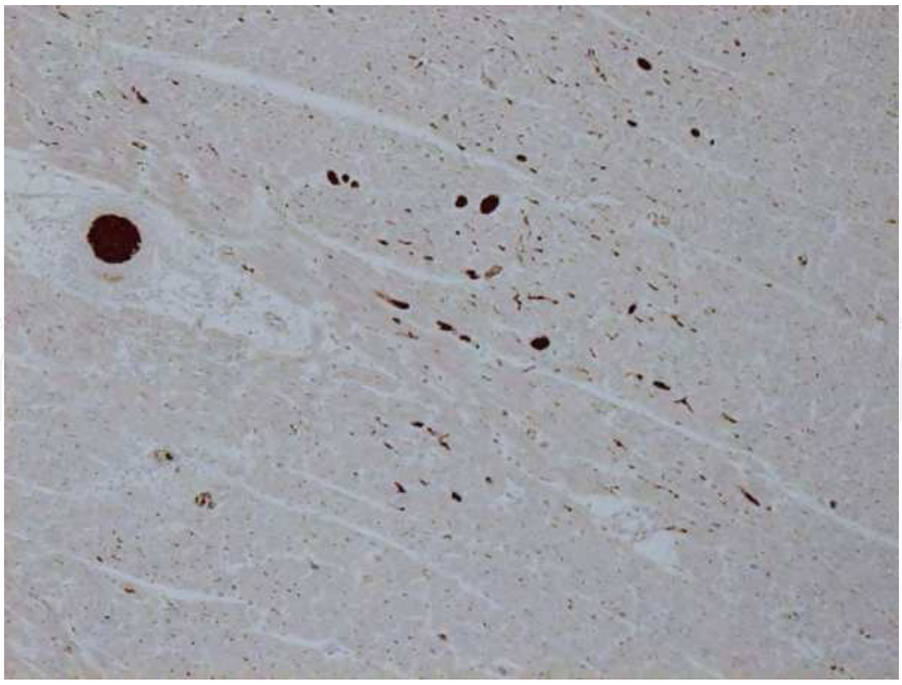

Fig. 7. Numerous emboli of fragments of platelet thrombi are observed in small arteries and capillaries at the distal portion of the left anterior descending artery. Immunohistochemistry for CD 42b.

8. Patients with STEMI

8.1 SRA index and CK, CK-MB, h-CRP

Abnormally increased levels of CK and CK-MB were observed in 53.8 % and 55.6% cases respectively at the hospitalization, and all cases showed abnormally high levels of CK and CK-MB within 24 hours after hospitalization. There was a strong correlation between CK and CK-MB (r=0.986), but no correlation between the SRA index and CK (r=0.025), CK-MB (r=0.005), and h-CRP(r=0.085) were seen (all, Student's t-test).

8.2 Pathological findings of thrombus

Thrombus was observed in 389 (99%) of the 393 patients, plaque contents alone were detected in 2, and neither thrombus nor plaque contents was identified in 2. In 270 patients, only thrombus was found; and both thrombus and plaque content were identified in 119. PT was found in 387 of 389 (99.5%) patients, MT in 269 (69.2%), FT in 57 (14.7%), and OT in 29 (7.5%). Results of the histopathological examination of thrombus are shown in table 1. RMT was detected in 300 (77.1 %) patients (Table 1). One type of contact was detected in 285 (73.3 %) patients, 2 types in 61 (15.7 %) and 3 types in 12 (3.0 %), and PT, or MT alone was found in 29 and 2 patients respectively. Contact between PT and OT was not observed. There was no gradual morphological transition from PT to MT or FT, but there were gradual transitions from MT to FT, and FT to OT in some cases.

Group	Contact Pattern	n	Thrombus n/n (%)	SRA index >30 n/n (%)
A	P	29	89/389(22.9)	46/89 (51.7)
	P-C	60		
B	M	2	243/389(62.5)	181/243(74.5)
	P-M	202		
	P-C+P-M	39		
C	P-F	23	57/389(14.7)	49/57(86.0)
	P-M+P-F	14		
	P-C+P-F	8		
	P-C+P-M+P-F	12		

Table 1. Brief title: Relationships between contact patterns of thrombus and SRA index at hospitalization[1].

[1]P: Platelet thrombus. P-C: Contact between platelet thrombus and plaque content. M: Mixed thrombus. P-M: Contact between platelet thrombus and mixed thrombus. P-F: Contact between platelet thrombus and fibrin-rich thrombus.

Eighty-nine patients were classified into group A, 243 into group B, and 57 into group C (Table 1). Typical findings of group A (P-C) are shown in figure 8. Macrophages in plaque content were positive for SRA, and SRA positive cells were not found in platelet thrombus. Figure 9 to 12 are typical findings of group B (P-M). Platelet thrombus is adhered on the mixed thrombus (Figure 9, 10), and fibrin mesh is not observed in platelet thrombus (Figure 11). SRA positive cells are infiltrated into mixed thrombus along the boundary zone (Figure 12). Typical findings of group C (P-F) are shown in figures 13 and 14. SRA positive cells are diffusely infiltrated in fibrin-rich thrombus (Figure 14). Fragments of PT are frequently found in MT in many cases (Figure 15). SRA^+ cells infiltrated into 147 (54.6%) of 269 MT. These cells and SRA^+ cells in PB were nearly equal in size, and infiltrated into MT along the boundary zone between PT and MT in most cases. SRA^+ cells were diffusely infiltrated into all FT and OT. Some of these SRA^+ cells were large in size. Foam cells in plaque content were positive for SRA. SRA^+ cells were not infiltrated into PT.

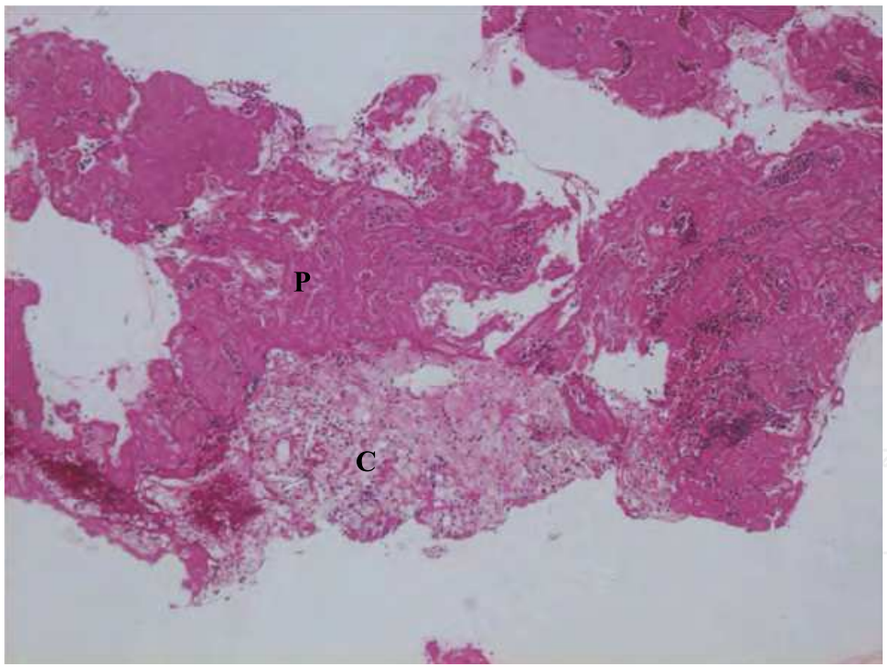

Fig. 8. Contact between platelet thrombus (P) and plaque content (C).

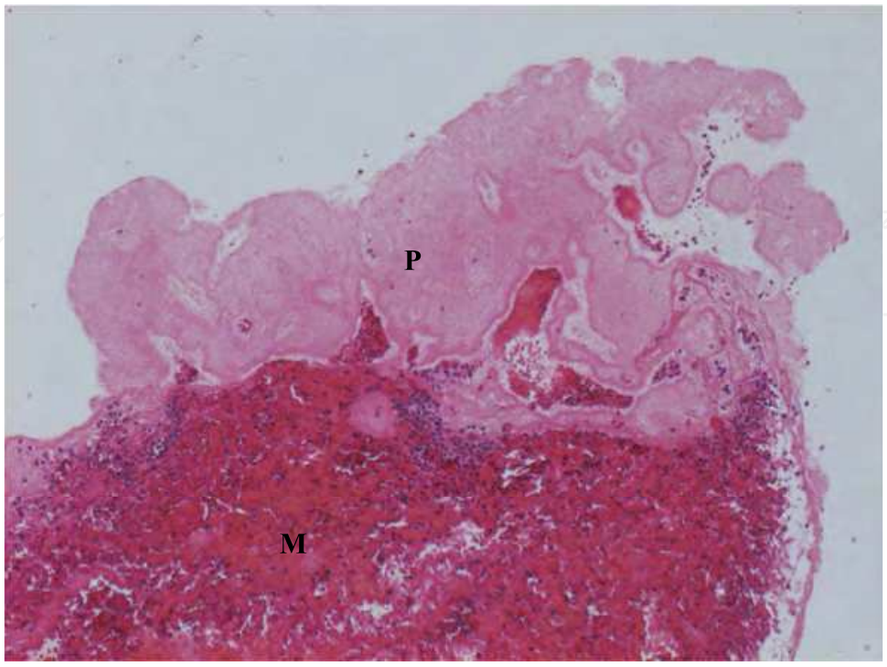

Fig. 9. Contact between platelet thrombus (P) and mixed thrombus (M).

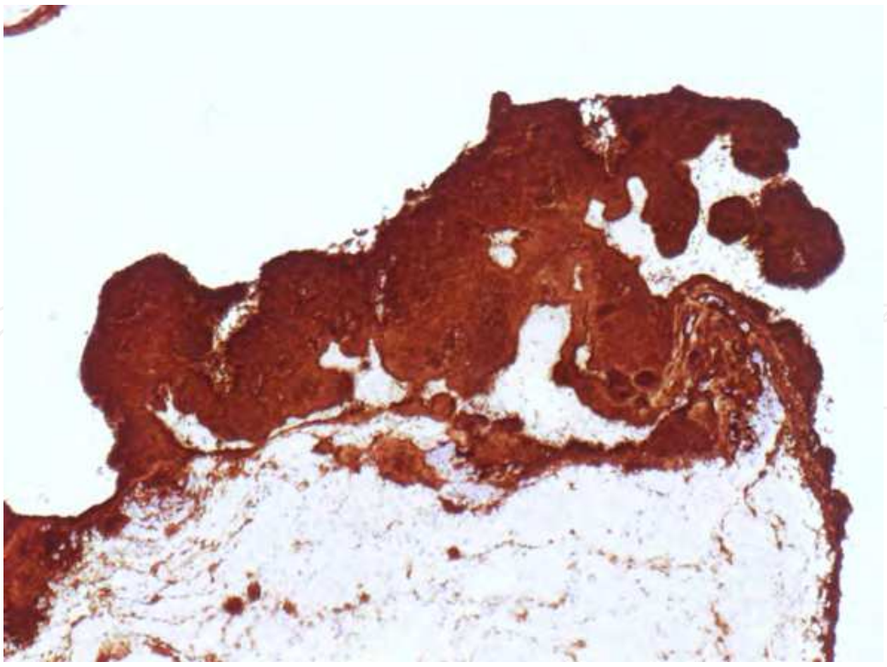

Fig. 10. Serial section of figure 9. Platelet thrombus is strongly stained. Immunochemistry for CD42b.

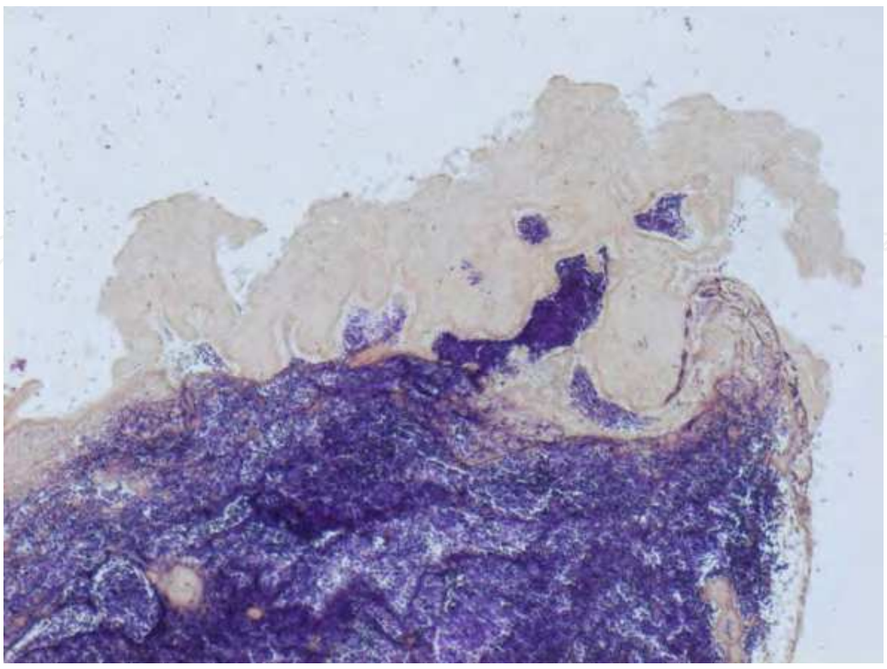

Fig. 11. Serial section of figure 9. Fibrin mesh is not observed in platelet thrombus. phosphotungstic acid hematoxylin stain.

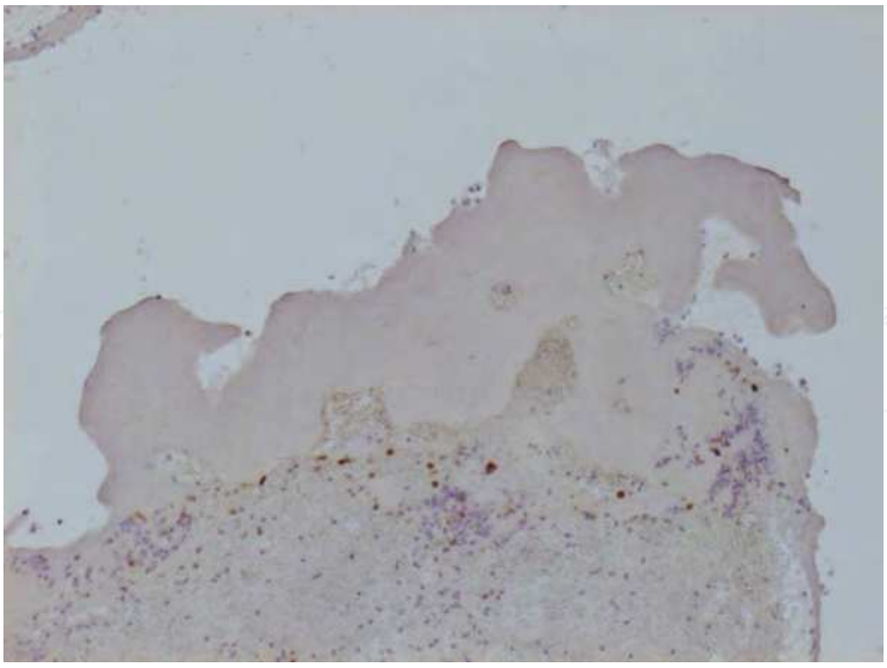

Fig. 12. Serial section of figure 9. Scavenger receptor A positive cells infiltrate into mixed thrombus along the boundary zone. Immunochemistry for CD204.

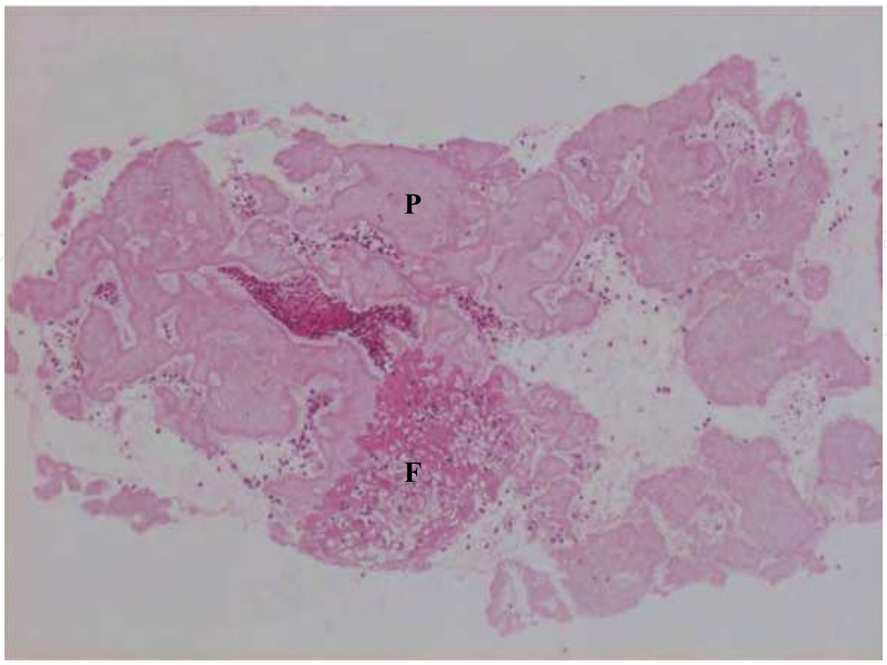

Fig. 13. Contact between platelet thrombus (P) and fibrin-rich thrombus (F).

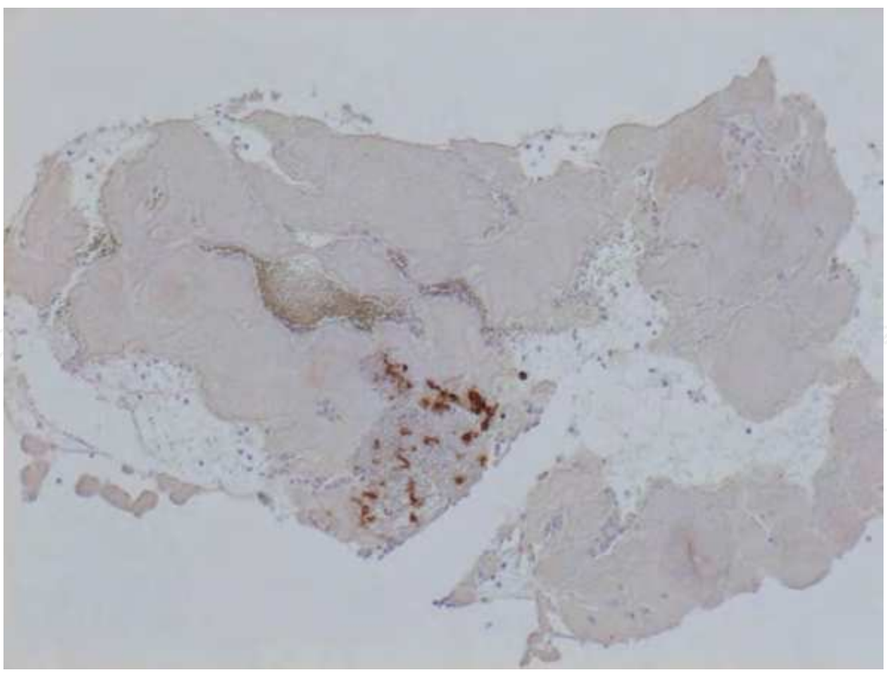

Fig. 14. Serial section of figure 13. Scavenger receptor A positive cells infiltrate into fibrin-rich thrombus. Immunochemistry for CD204.

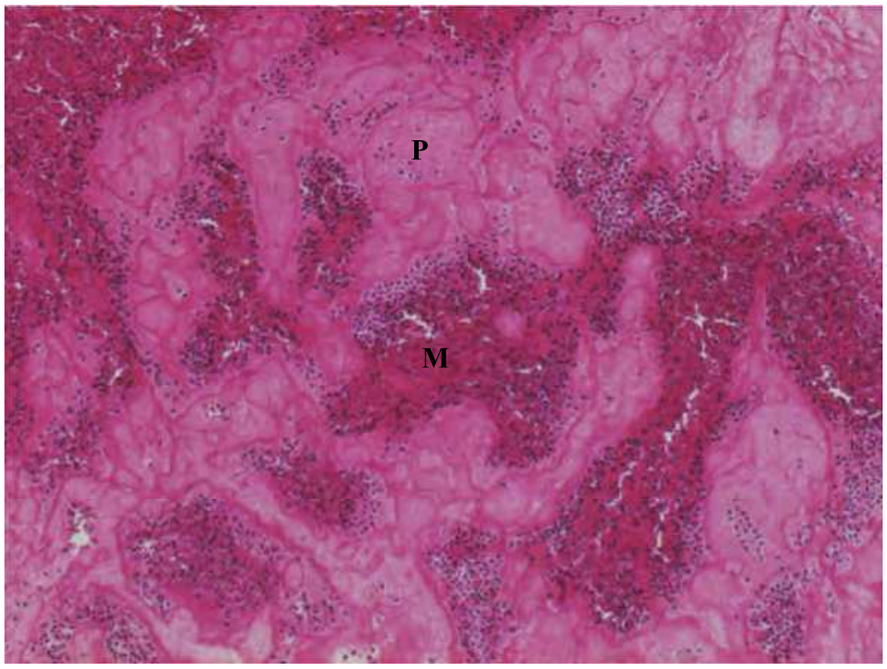

Fig. 15. Small fragments of platelet thrombus (P) are intermingled with mixed thrombus (M).

8.3 SRA$^+$ cells in PB

SRA$^+$ cells were observed in all control cases and in all patients with STEMI and UA. Neither SRA$^+$ large macrophages nor foamy cells could be observed in PB of all examined cases. SRA index of control cases ranged 1 to 24 (mean±SD=11.1±7.5). The relationships between SRA index and contact patterns of thrombus at hospitalization were shown in table 1. At hospitalization, SRA index exceeded 30 in 276 of 393 patients with STEMI (Figure 16). Thrombus was identified in all these patients with more than 30 SRA index. PT was identified in 274 (99.3 %), and RMT in 230 (83.3 %) cases. From the viewpoint thrombus, SRA index exceeded 30 in 230 of 300 (76.7 %) cases with RMT and 46 of 89 (51.7 %) cases with PT alone (Table 1). The percentage of patients with a SRA index more than 30 was significantly lower in group A patients than other groups of patients (P<0.001). Significant differences were observed between group A and B, and A and C (both, P<0.001).

Peripheral blood of 109 of 117 patients with less than 30 SRA index at hospitalization were examined repeatedly, and SRA index of all 109 cases exceeded 30 within 2 to 3 days after hospitalization. The maximum SRA indices of STEMI patients during 3 days after hospitalization were significantly higher than those of STEMI patients at hospitalization.

The SRA index of 60 of 79 UA (75.9%) cases were 30 or more at hospitalization. The differences in the SRA index were not significant between STEMI and UA (Table 2, P=0.218, Welch's test).

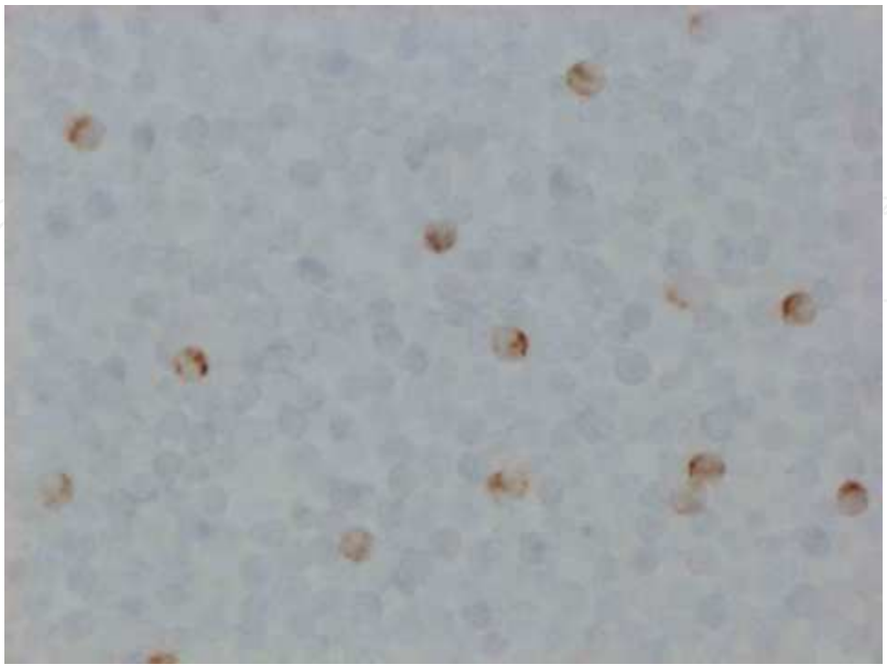

Fig. 16. Scavenger receptor A positive cells in peripheral blood (SRA index: 187/10HPFs).

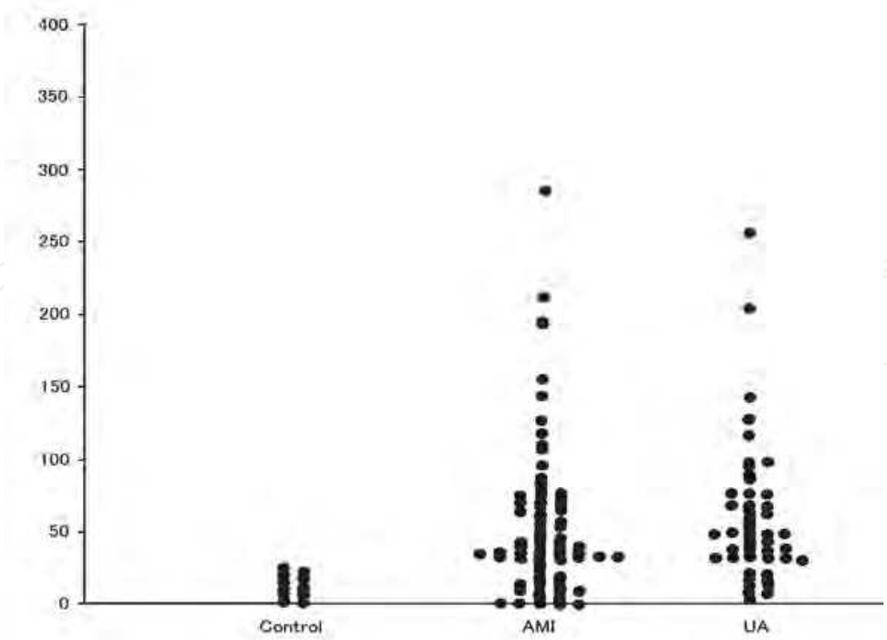

Table 2. The scattered plots of the SRA index of controls, AMI, UA.

9. Differentiation of SRA$^+$ cells in PB

It is reported that freshly isolated blood monocytes were negative for SRA [25]; however, a few reports have indicated that SRA$^-$monocytes can differentiate into SRA$^+$ cells in PB by various stimuli [32, 33, 34]. SRA$^+$ cells were observed in all control cases. We , therefore, surmised that a small number of SRA$^-$ monocytes differentiated into SRA$^+$ cells in PB of healthy men and women by various stimuli. Fuster et al. classified the progression of coronary atherosclerotic diseases into five phases [35]. Phase 1 is represented by a small plaque that is present in most people under the age of 30 years. We set the normal upper limit of the SRA index at 30 [27], since plaque disruption, fissure, or erosion and RMT might not develop in healthy men and women in their 20s, and SRA index of these control cases ranged 1 to 24 (mean±SD=11.1±7.5).

We considered two possibilities on the pathophysiologic mechanisms underlying the differentiation of SRA$^+$ cells in patients with STEMI (myocardial infarction or plaque disruption, fissure or erosion). With the recognition that atherosclerosis is an inflammatory process [36], h-CRP has been evaluated as a potential tool for predicting the risk of AMI [37, 38, 39], and CK and CK-MB are good markers of myocardial injury. Macrophages are known to arise from monocytes, and become larger over twice as large as monocytes with differentiation. SRA$^-$monocytes became positive for SRA after 5 days in culture with M-CSF [40], and differentiated into large macrophages by 10 days [41]. Cytokines elevate in PB after insult [42]. Myocardial infarction is severe insult, so SRA$^+$ cells may increase in PB as a result of myocardial infarction. However, differentiation of SRA$^+$ cells in PB was not considered to result from myocardial injury, because there was no correlation between SRA indices and CK, CK-MB, and h-CRP.

The differentiation of SRA$^-$ monocytes into SRA$^+$ macrophages was believed to take place in atherosclerotic lesions by stimulation of M-CSF [21-24]. Disruption, fissure or erosion of an atherosclerotic plaque is generally recognized as a proximate event responsible for the development of the ACS [8-12]. The SRA index of the patients with less than 30 SRA index at hospitalization rapidly increased, and the SRA index of all these STEMI patients exceeded 30 within 2 to 3 days. We therefore surmised that SRA$^-$ monocytes might differentiate into SRA$^+$ cells as the result of exposure of plaque content that contains M-CSF to the blood stream.

10. Coronary occlusion

Examinations of aspirated material have focused on thrombus age [31, 43, 44]. Rittersma et al. classified thrombi into 3 groups: fresh (< 1 day), lytic (1 to 5 days), and organized thrombus (> 5 days) [31]. However it is hard to understand the constituents of thrombus by this classification. PT and some MT seem to correspond to fresh thrombus, and some MT and FT to lytic thrombus. PT was detected in 387 (99.5 %) of 389 patients, MT in 269 cases (69.2 %) and FT in 57 (14.7 %). SRA$^+$ cells infiltrated into all FT and 147 (54.6 %) of 269 MT, but not PT. These SRA$^+$ cells in PB were thought to be infiltrated into MT, since SRA$^+$ cells infiltrated in MT along the boundary zone between PT and MT (luminal side of the coronary artery). From these findings, PT was considered to be most fresh thrombus, and infarct-related coronary artery was totally and rapidly occluded by the formation of PT.

Using their computer-assisted extracorporeal-perfusion system, Badimon et al.[45] and Lassila et al.[46] found that platelet deposition increased significantly with increased stenosis. Sudden

coronary occlusion was often preceded by a period of plaque instability and thrombus formation, initiated days or weeks before the onset of symptoms [15-18], and total coronary occlusion of the infarct-related artery always results from the growth of RMT [44, 47 - 49]. Considering these reports and the histopathological findings of thrombi, PT was thought to be formed abruptly as a result of severe coronary stenosis due to sudden extrusion of atheromatous debris into vessel lumen in 43 group A patients with a SRA index less than 30 at hospitalization, and due to gradual growth of RMT in group B and C patients. The percentage of patients with SRA index more than 30 at hospitalization was significantly lower in group A patients than other groups of patients. This finding seemed to support the theory, since the SRA index exceeded 30 about 2 days after plaque disruption[27].

11. The fate of platelet thrombus

RMT was observed in 300 of 389 STEMI cases. Meshwork of fibrin was observed in RMT, so RMT was thought not to be fragile. RMT predisposes patients to recurrent thrombotic vessel occulusion[15-17], and plaque disruption, fissure or erosion with thrombus contributes to plaque development and progression[18]. Gradual growth of RMT plays an important role on the increased stenosis of coronary artery, and total occlusion of coronary artery by platelet thrombus.

Meshwork of fibrin was not contained in platelet thrombus. Consequently, platelet thrombus was considered to be very fragile. Fragments of platelet thrombus were frequently observed in mixed thrombus and numerous emboli of fragments of platelet thrombus were observed in small arteries and capillaries at the distal portion of the infarct related artery of autopsy cases. Platelet thrombus was considered to repeat formation and disintegration with the gradual growth and lysis of RMT, and numerous emboli of fragments of platelet thrombus at the distal portion of the infarct related artery may repeatedly injure cardiac myocytes .

12. SRA index and vulnerable plaque

Disruption, fissure, or erosion of an atherosclerotic plaque, with RMT has a fundamental role in the pathogenesis of acute coronary syndromes (ACS) [8-12].

In general, in case of AMI, a direct relationship between the onset of plaque disruption and acute transmural ischemia is assumed; however pathological studies of autopsy [13, 14] and thrombectomy [18, 31, 43] materials indicated that plaque disruption, fissure or erosion with RMT remain clinically silent days or weeks before the fatal event. The SRA index of the patents with less than 30 SRA index at hospitalization exceed normal level within 2 to 3 days. These findings indicated that SRA index rapidly increases in AMI patients after plaque disruption, erosion, or fissure. A SRA index more than 30 was observed in patients with multiple organ dysfunction syndrome[50]. Therefore, SRA index more than 30 was not a specific finding to ACS. SRA index exceeded 30 in 230 of 300 (76.7 %) cases with RMT and 46 of 89 (51.7 %) cases with PT alone, and 276 of all 389 cases at hospitalization. Thrombus was identified in all 276 patients with a SRA index more than 30 at hospitalization. PT was detected in 99.3 % and RMT in 83.3 % of these patients. SRA index did not exceed 30 in healthy control cases. SRA index of these 276 patients was surmised to exceed 30 before the onset of STEMI. The SRA indices of 75.9 % of unstable angina cases were more than 30 at hospitalization [27]. The pathophysiological substrate of the unstable angina is now considered

to be common with the acute myocardial infarction. We, therefore, believe that the abnormal increase of SRA^+ cells is considered to be a useful finding to gather the presence of disrupted or fissured or eroded plaque, PT, and probably RMT in patients with UA.

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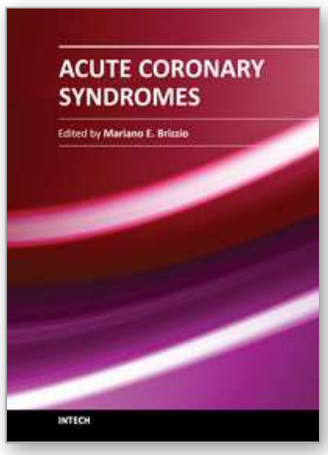

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This book has been written with the intention of providing an up-to-the minute review of acute coronary syndromes. Atherosclerotic coronary disease is still a leading cause of death within developed countries and not surprisingly, is significantly rising in others. Over the past decade the treatment of these syndromes has changed dramatically. The introduction of novel therapies has impacted the outcomes and surviving rates in such a way that the medical community need to be up to date almost on a "daily bases". It is hoped that this book will provide a timely update on acute coronary syndromes and prove to be an invaluable resource for practitioners seeking new and innovative ways to deliver the best possible care to their patients.

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