

Rheological Abnormalities and Thromboembolic Complications in Heart Disease: Spontaneous Echo Contrast and Red Cell Aggregation

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ABSTRACT

The role of abnormal rheological changes in the pathogenesis of thromboembolism has received much attention in recent years, especially in the field of cardiology. Such changes are sometimes seen in an echocardiogram as a smokelike haze known as spontaneous echo contrast (SEC). The presence and severity of SEC correlate with dilated cardiac chambers and the incidence of thromboembolic complications. It is caused by increased red cell aggregation and increased fibrinogen levels, both of which are known risk factors for thrombosis. Although not used clinically, measurements of red cell aggregation can be made in research settings. This can provide findings that give insight into factors causing increased red cell aggregation. A small series of patients with angina pectoris was studied with the Myrenne aggregometer for red cell aggregation. The results, which show correlation between the plasma fibrinogen and triglyceride levels, are presented. As yet, there are only a few therapeutic guidelines for the correction of abnormally high fibrinogen levels in patients at risk.

KEYWORDS: Fibrinogen, red cell aggregation, spontaneous echo contrast, viscosity, thromboembolism

Objectives: On completion of this article, the reader should be able to (1) appreciate the meaning of echo contrast and its relationship to thromboembolism and (2) define the role of red cell aggregation in cardiovascular disorders.

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The Hyperviscosity Syndromes; Editor in Chief, Eberhard F. Mammen, M.D.; Guest Editor, Hau C. Kwaan, M.D., Ph.D. *Seminars in Thrombosis and Hemostasis*, volume 29, number 5, 2003. Address for correspondence and reprint requests: Hau C. Kwaan, M.D., 333 East Huron Street, Chicago, IL 60611. E-mail: h-kwaan@northwestern.edu. ¹Professor of Medicine, ²Hematology and Oncology Division, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; ³Matsumoto General Hospital, Matsumoto, Japan. Copyright © 2003 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. 0094-6176,p;2003,29,05,529,534,ftx, en;sth00916x.

Hypercholesterolemia, hypertension, diabetes mellitus, and cigarette smoking are widely recognized as major risk factors for cardiovascular disease. However, the pathogenic elements associated with these risks have received less attention.¹ Increased whole-blood viscosity and red blood cell aggregation have been observed in patients with these risk factors.²⁻⁵ In addition, a high fibrinogen level has also been recognized as a risk factor for coronary artery disease and stroke. Of significance is the fact that blood viscosity is related to the fibrinogen level.⁶⁻⁸ In this article, recent observations of abnormal echographic findings that are indicative of increased thromboembolic risks will be reviewed. Because red cell aggregation is believed to be the cause of these echographic abnormalities, red cell aggregation measurement in patients with ischemic heart disease will also be presented.

SPONTANEOUS ECHO CONTRAST

As a result of the widespread use of echocardiography in the diagnosis of heart diseases, an interesting observation of the videodensity in the cardiac chambers has been made. A swirling, dense, smokelike haze of variable intensity is sometimes seen. Such abnormal videodensities are termed spontaneous echo contrast (SEC).^{9,10} Figure 1 shows SEC in the right atrial appendage of a patient with atrial fibrillation (in the left panel). It can be detected by either transthoracic or transesophageal echocardiography. Several methods of grading the intensity of SEC are available. It can be graded objectively as mild, moderate, or severe by more than one independent observer. Alternatively, echocardiographic images recorded on videotape can be digitized into gray-scale levels

and the videodensity can be measured.¹¹ A third method is by acoustic densitometry with integrated backscatter using a computerized software program incorporated in the echo equipment.^{12,13} Studies by these various methods showed that SEC is correlated with enlarged chambers, such as the left atrium in mitral stenosis,¹⁴ dilated ventricles in cardiomyopathy and apical aneurysm,¹⁵ and atrial fibrillation.¹⁶ SEC can also be seen in the aorta. They appear as dynamic smokelike echoes within the descending thoracic aorta and have the characteristic swirling motion, similar to that seen in SEC in the cardiac chambers.^{17,18} The severity of the SEC has also been observed to be correlated with the incidence of stroke,¹⁹ intra-atrial thrombus,¹⁴ other thromboembolic events,^{19,20} and even with survival.²⁰ In a retrospective study of 42 stroke patients, left atrial SEC was present in 21%, but it was present in only 2% of healthy controls.²¹ In another prospective study of 50 stroke patients, the presence and severity of left atrial SEC were correlated with the size of the left atrium and with atrial fibrillation.²² Likewise, aortic SEC was associated with increased thromboembolic risks.²³⁻²⁶ The presence and severity of SEC have also been correlated with increased blood fibrinogen levels and whole-blood viscosity or plasma viscosity.^{22,27} Other abnormal laboratory findings concerning coagulation and fibrinolytic parameters were also found in patients with SEC.¹⁸ A number of in vitro studies revealed that SEC can be reproduced when red cell aggregates are experimentally induced.^{28,29} The severity of SEC in vitro is again correlated with the fibrinogen concentration. Because increased fibrinogen level,^{30,31} and in some cases abnormal fibrinogen,³² can cause red cell aggregation, these in vitro observations shed some light on why fibrinogen is a well-known risk factor for

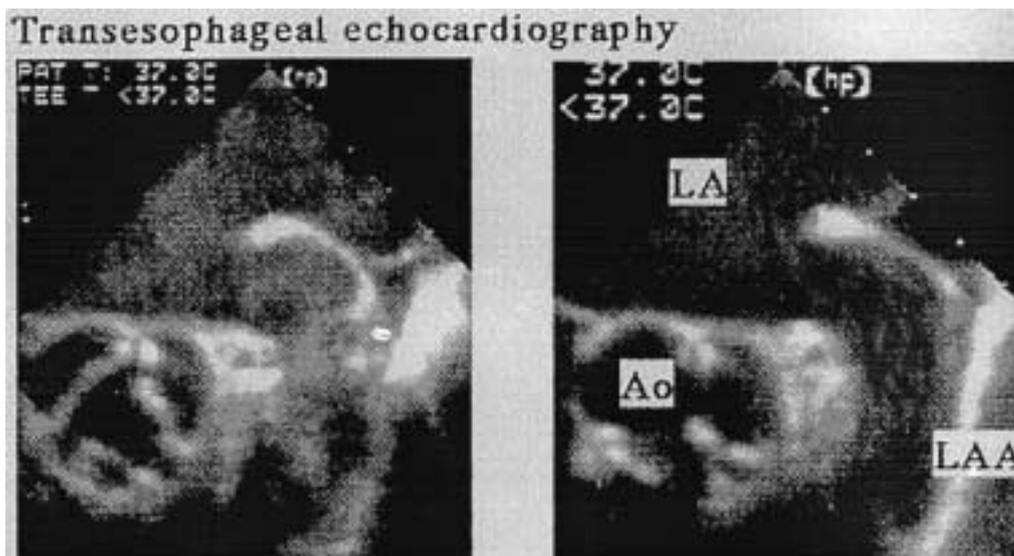


Figure 1 Transesophageal echocardiogram showing the presence of spontaneous echo contrast as a white haze in the left atrial appendage (LAA) in the left panel and its disappearance 24 hours after the administration of a defibrinating agent batroxobin in the right panel. (Reprinted with permission from Seiji et al.²⁷)

stroke and thrombotic cardiovascular events. The administration of a defibrinating agent batroxobin, derived from the venom of the Brazilian viper *Bothrops atrox*, in 36 patients with atrial fibrillation was able to lower their blood fibrinogen levels and their whole-blood viscosity while diminishing the SEC in their echocardiograms.²⁷ In the echocardiogram shown in Figure 1, the SEC disappeared after the patient was given batroxobin (right panel). Other attempts have been made to reduce fibrinogen-induced red cell aggregation, including the use of another defibrinating agent, anicrod, derived from the venom of the Malaysian viper *Akistrodon rhodostoma*³² and of low-molecular-weight dextran (dextran-40).²⁸ Although other drugs such as the fibrates have been known to lower fibrinogen,^{33,34} and thus may have an effect on the red cell aggregation, they have not been tried clinically.

RED CELL AGGREGATION

In addition to its contribution to the formation of SEC, red cell aggregation is a major player in the microangiopathy in diabetes³⁵ and in the development of deep vein

thrombosis.^{36,37} However, in the patient with ischemic heart disease, increased red cell aggregation has been observed and considered a predictor of unfavorable clinical outcome in patients with acute coronary syndrome.³⁸⁻⁴⁰

A number of methods have been employed to quantitate red cell aggregation.⁴¹⁻⁴³ One such method is performed with the Myrenne aggregometer (Myrenne, Roetgen, Germany). The aggregation in a suspension of red cell sample is measured by the amount of light transmitted. This red cell suspension is subjected first to a high shear rate (600 s^{-1}) to disperse all preexisting aggregates (Fig. 2). After disaggregation, the shearing is stopped (shearing rate = 0 s^{-1}) (M mode). This results in a sudden drop of light transmission because of the loss of orientation and the elongation of the red cells. The light transmission at this point is expressed as aggregation index at M mode (AI_M). Then, at a low shear rate, the red cell aggregates will reform and can be recorded as a return of light transmission. Over the next 10-second period, the light transmission is plotted as area under the curve and expressed as aggregation index at M-1 mode (AI_{M-1}).

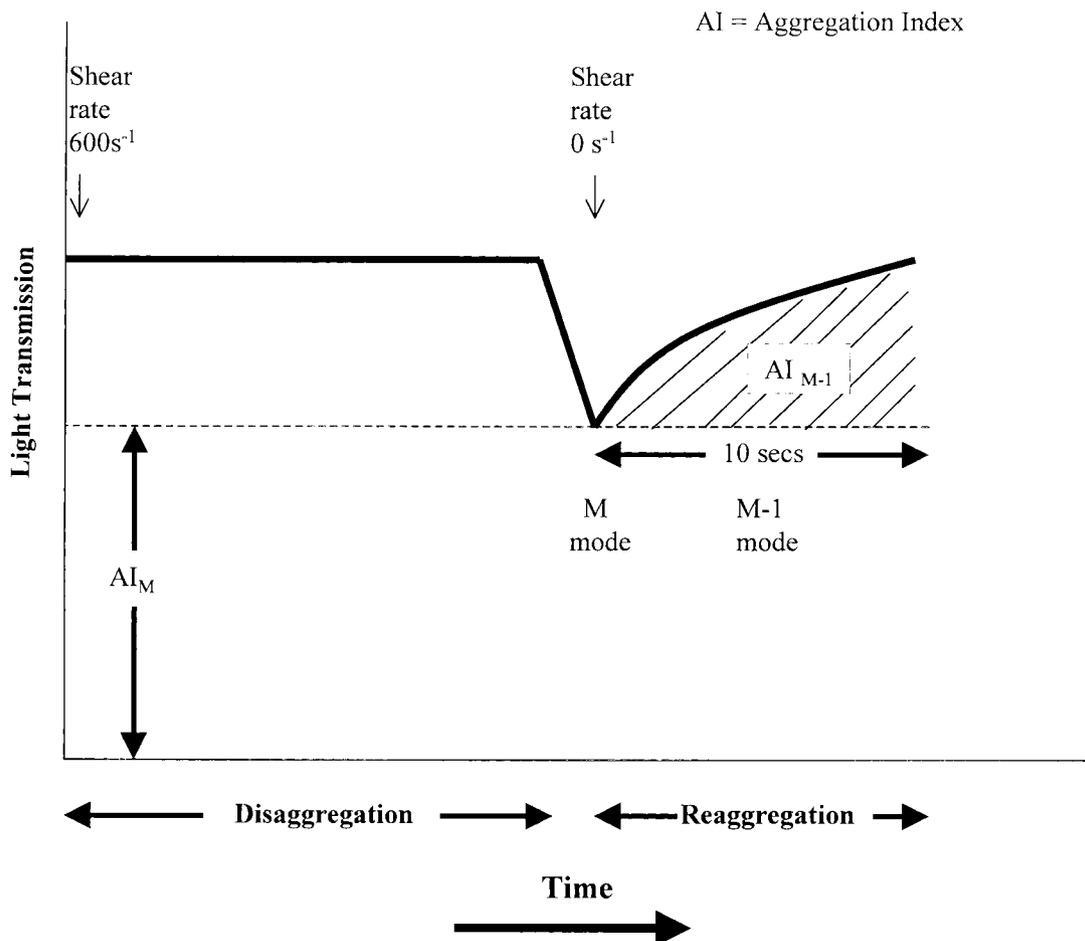


Figure 2 The measurement of red cell aggregation as a function of light transmission using the Myrenne aggregometer. (See text for details.)

Table 1 Characteristics of the Two Study Groups: Patients with Angina Pectoris and Healthy Controls

	Angina Pectoris	Healthy Control	P
Male	24	10	
Female	5	6	
Age (years)	71.2 ± 7.8	65.1 ± 6.7	< 0.05
AI _{M-1} (M-1 mode)	29.1 ± 5.0	24.9 ± 7.5	< 0.05
Fibrinogen (mg/dL)	324.4 ± 79.1	257.8 ± 73.5	< 0.01
RBC (× 10 ⁶ /μL)	4.04 ± 0.64	4.31 ± 0.39	
Hgb (g/dL)	12.8 ± 1.9	13.6 ± 1.3	
T-cholesterol(mg/dL)	187.8 ± 49.2	186.4 ± 49.5	
Triglyceride (mg/dL)	142.0 ± 65.2	126.8 ± 71.5	
Medication (%)			
Antiplatelet	69.0	12.5	
Antihypertensive	58.6	37.5	
Statin	48.3	0	
Insulin	6.9	0	

Red cell aggregation was studied using the previously described method by one of the authors (S.S.) in 29 patients with stable angina pectoris who angiographically had significant coronary artery stenosis and in 16 healthy controls. Their red cell count and hemoglobin and their levels of fibrinogen, triglycerides, and total cholesterol were also measured. The results showed that there was an increase in red cell aggregation in the angina group compared with the controls (AI_{M-1} = 29.1 ± 5.0 versus 24.9 ± 7.5; P < 0.05) (Table 1). The fibrinogen levels of the angina group were significantly higher than those in the control group were (324.4 ± 79.1 mg/dL versus 257.8 ± 73.5 mg/dL; P < 0.01). The triglyceride levels of the angina group were significantly higher than those in the control group were (142.0 ± 65.2 mg/dL versus 126.8 ± 71.5 mg/dL; P < 0.05). Both the higher fibrinogen and the higher triglyceride levels likely contribute to the increase in red cell aggregation. This is demonstrated by further analysis, showing that there was a significant correlation between the red cell aggregation and the fibrinogen level in both groups (P < 0.01) and also a significant correlation between red cell aggregation and triglyceride level (P < 0.01) (Fig. 3). This finding also confirmed previous observations of increased red cell aggregation in primary hypertriglyceridemia.⁴⁴ Although small molecules do not induce red cell aggregation, the alteration of plasma triglyceride level changes in the red cell membrane lipid composition can influence the red cell aggregation.⁴⁵

Fibrinogen also has many pathogenetic functions related to the development of atherosclerotic lesions and the onset of acute vascular events.⁷ Our data and previous reports show that fibrinogen is also a major factor in producing abnormal rheological characteristics.

Patients with unstable angina and acute myocardial infarction have been found to have increased red cell aggregation and whole-blood viscosity.⁶⁻⁸ The inflammatory process is a major component in different stages of atheroma formation and in local events leading up to the rupture of atherosclerotic plaque.⁴⁶ The associated increased fibrinogen follows as an acute phase reactant. Because an increase in fibrinogen leads to more red cell aggregation, the latter may also increase the viscosity of blood, resulting in decreased local blood flow. This may also conceivably contribute to the pathogenesis of acute myocardial infarction. Inflammation also results in other changes. Increased vascular permeability results in the extravasation of fluid leaving a diminished plasma content. Proteins of small molecular sizes, such as albumin, extravasate with the fluid component whereas large molecules, such as macroglobulin, remain. A higher concentration of macromolecules increases red cell aggregation. Depending on the degree of vascular permeability, fibrinogen may or may not extravasate. Soluble fibrinogen complexes are less likely to extravasate than is normal fibrinogen.

In coronary artery stenosis with partial occlusion, there is aberrant blood flow in the poststenotic segment of the vessel, creating local vortices with low shear rates. This can result in increased viscosity. In complete occlusion, there is zero flow in the poststenotic segment. In this region, the red cell aggregation can contribute to thrombogenesis. As a result, if the obstruction is relieved subsequently by angioplasty or by stenting, the resumption of blood flow may be less than expected. It is conceivable that red cell aggregation can also be responsible for the failure of reperfusion in the microvasculature beyond the occlusion.

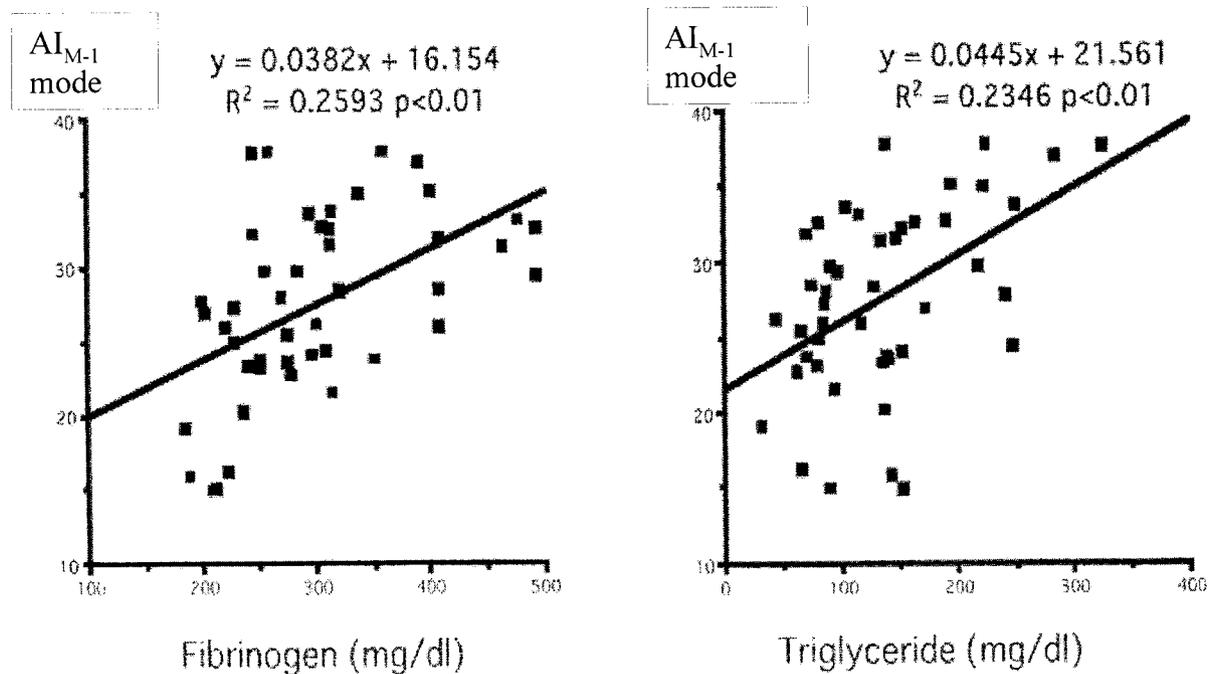


Figure 3 The correlation between the plasma fibrinogen level (left graph) as well as the triglyceride level (right graph) and the red cell aggregation measured as AI_{M-1} , as described in the text.

CONCLUSION

In conclusion, increased viscosity is an important component of ischemic heart disease. Various factors contributing to viscosity, such as increased red cell aggregation, inflammatory changes, and vascular permeability, have received greater attention in recent years. Increased plasma fibrinogen levels, a well-recognized risk factor, is now looked on with a new light for its property of causing red cell aggregation and therefore increasing viscosity. Although sophisticated methods for the assessment of red cell aggregation are available in the research laboratory, an accurate means for the detection for red cell aggregation that can be applied in clinical cardiology practice remains to be developed.

ACKNOWLEDGMENT

The authors acknowledge the valuable assistance of Ivy Weiss in the preparation of the manuscript.

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