# Editorial comment
# Significance of multiple coronary artery thrombi. A consequence of diffuse atherosclerotic disease?

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(Ital Heart J 2000; 1 (12): 832-834)

The opinions expressed in this editorial comment are not necessarily those of the Editors of the Italian Heart Journal.

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In this issue, Garbo et al.[1] demonstrate convincingly the occurrence of multiple acute thrombi in 4 patients presenting with acute myocardial infarction. In their patients, multiple thrombosis was documented by angiographic findings and resolution of electrocardiographic changes only after stenting of multiple segments. The report is anecdotal, and unfortunately does not hint at the clinical incidence of multiple coronary thrombosis among patients undergoing angiography.

The occurrence of multiple acute thrombi has been documented in careful autopsy studies of ischemic death, but the incidence varies from series to series. Falk[2] demonstrated 51 recent thrombi in 42 hospitalized patients with ischemic heart disease and chest pain before death, and Davies and Thomas[3] found 115 intraluminal thrombi in 74 hearts from sudden cardiac death victims, suggesting that one-fourth to one-half of lethal acute thrombi are multiple. However, if one looks at the definition of acute thrombus in these series, a lower overall rate seems to emerge. Falk[2] reports an incidence of 103 plaque ruptures in 44 patients. However, in 63 of these, there was intimal hemorrhage without luminal thrombosis or there was a "tiny mural thrombus sealing the rupture site". Forty cases had significant luminal thrombi and of these, 38 were occlusive. Forty-four of the 74 cases reported by Davies and Thomas[3] had major thrombi occupying more than 50% of the lumen. However, the authors state that 42 of 44 and at 103 of 115 thrombi had coexisting intraintimal thrombus, which they say resulted form fissuring. Often, this means hemorrhage into a plaque, which is not necessarily associated with luminal thrombus. Thus, it is unclear if the lesion described is a true luminal thrombus at two different sites.

Arbustini et al.[4] demonstrated multiple thrombi in less than 10% (27 of 291 hearts) of patients dying with acute myocardial infarction complicating coronary thrombosis. In our laboratory, the rate of multiple coronary thrombi in sudden coronary death is even lower[5] (less than 10%), reflecting our relatively low overall rate of coronary thrombosis in an out-of-hospital population, and when applying strict criteria for luminal thrombi only and not intraplaque thrombi.

The characteristics of patients with multiple coronary thrombi have not been well studied. The patients in the study of Garbo et al.[1] were predominantly male (3 of 4) with multiple risk factors. Arbustini et al.[4] did not characterize their patients with multiple thrombi, but did not note a difference in the rate of multiple thrombi secondary to plaque ruptures as compared to those caused by plaque erosions. In a series of sudden deaths in men[6] and women[7], we did not identify multiple ruptures in patients with erosions, but found multiple ruptures in 3 of 49 men with one or more ruptures (6%), and 1 of 8 women with one or more ruptures (13%) (Fig. 1). Therefore, our incidence of multiple thrombi is closer to that reported by Arbustini et al., and is more likely the true incidence. All of the men with multiple ruptures were smokers with severe dyslipidemia (total:high density lipoprotein cholesterol ratio > 8) and 2 of 3 had type 2 diabetes mellitus. The lone woman had moderate dyslipidemia (total:high density lipoprotein cho-

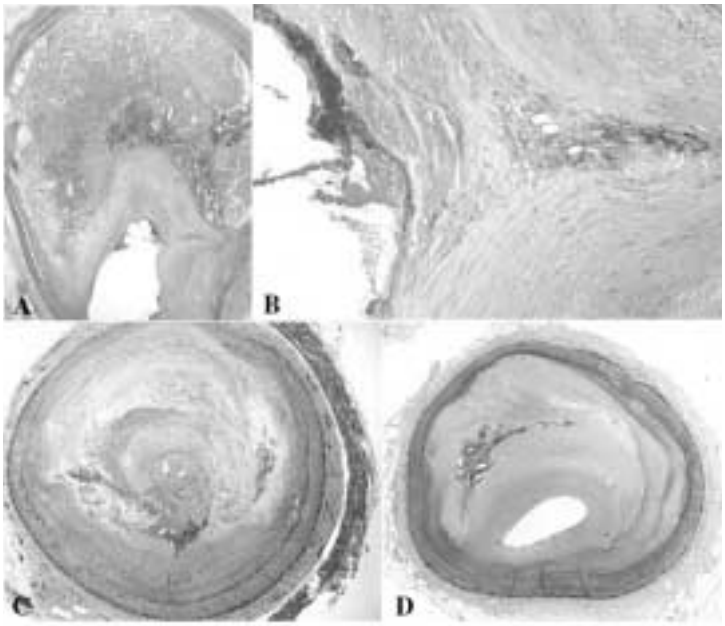


**Figure 1.** *Multiple plaque ruptures in a case of sudden ischemic death.* A *demonstrates a plaque with a large lipid rich hemorrhagic core (left main coronary artery).* B, *a higher magnification of* A, *demonstrates a small mural thrombus. The culprit thrombus is shown in* C, *which occluded the circumflex artery. In the right coronary* (D) *was a healed plaque rupture (note concentric neointimal proliferation). All sections stained with Movat pentachrome.*

lesterol ratio 5.8), but did not smoke or demonstrate evidence of glucose intolerance.

What are the implications of the finding of multiple coronary thrombi in patients with acute coronary syndromes? Certainly, as the paper of Garbo et al.[1] illustrates, the cardiologist should be aware of the possibility of multiple thrombi in patients presenting with unstable angina and acute myocardial infarction. If all segments with acute thrombus are not stented or if free flow not established, the patient may not demonstrate complete resolution of symptoms, and electrocardiographic evidence of ischemia may persist. Although the data are few, there appears to be an association between multiple thrombi and acute plaque ruptures, especially in patients with multiple risk factors of smoking, dyslipidemia and glucose intolerance.

The surprisingly high apparent rate of multiple coronary thrombi in acute coronary syndromes may provide clues to the nature of progression of coronary atherosclerosis, as the acute coronary thrombi which brings the patient to the care of the physician may be but the tip of the iceberg. Arbustini et al.[8] have suggested that acute thrombi are present even in patients who die of non-coronary causes. The fact that acute coronary thrombi are fairly common and often multiple suggests that a large proportion of them go unnoticed; the fate of these silent ruptures has largely been unexplored.

The features of coronary thrombi that make them result in myocardial infarction are not clearly understood, although it has been demonstrated that lethal thrombi are often occlusive and occur in severely stenotic arteries[2]. In a series of hearts from sudden death victims, we have demonstrated that healed plaque ruptures are quite frequent in male victims of sudden coronary death, and that they provide proliferating compartments of the plaque that may actively contribute to plaque expansion[6]. These silent ruptures occur in all arterial segments. In contrast to acute ruptures which kill the patient, they occur at an earlier stage of plaque progression, at which time the arterial stenosis is relatively mild, and do not result in the marked expansion of the internal elastic lamina, as do acute ruptures. The fate of the mural thrombus after subclinical plaque rupture is likely a combination of extrusion with or without embolization into the microcirculation[2], and incorporation and enlargement of the plaque as organized thrombus.

What we are beginning to understand is that coronary thrombosis is an evolutionary process that does not simply arise suddenly in association with an acute coronary syndrome, and subsequently disappear with spontaneous or iatrogenic thrombolysis. Coronary atherosclerosis is characterized by ongoing thrombosis, often in several segments of the coronary tree simultaneously, which may be at different stages of organization and propagation. The factors initiating a thrombus that may lead to myocardial ischemia are undoubtedly multiple, and include degree of underlying stenosis, plaque composition allowing for positive remodeling, vasospasm, thrombus composition followed by distal embolization, propagation with involvement of branch points and collateral vessels, and genetic factors. The complex nature of coronary thrombosis undoubtedly accounts for the variety of clinical expressions of myocardial ischemia, from stable angina through unstable angina and acute myocardial infarction.

The findings of Garbo et al. that acute coronary thrombi in myocardial infarction may be multiple un-

derscore our need to understand more fully the mechanisms of ischemia that results from thrombotic occlusion of coronary vessels. Multiple thrombi may be explained on the basis of the diffuse nature of the atherosclerotic disease process involving multiple segments of coronary, aortic and carotid arteries. Why one thrombus may be silent, contributing insidiously to plaque progression without clinical symptoms, and why another causes myocardial infarction or sudden death are questions which deserve our top priority.

## References


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