Embolic Myocardial Infarction as a Consequence of Atrial Fibrillation
A Prevailing Disease of the Future

Frank D. Kolodgie, PhD; Renu Virmani, MD; Alok V. Finn, MD; Maria E. Romero, MD

A cute myocardial infarction (AMI) is a major cause of death and disability worldwide. When spontaneous AMI occurs, there is a >90% chance that the underlying etiology is primarily due to coronary events such as plaque rupture, erosion, or dissection referred to as myocardial infarction (MI) type 1. MI can also occur secondary to an ischemic insult in the absence of overt coronary artery disease (CAD), by an imbalance between myocardial oxygen supply and demand termed type 2 MI, which embodies a myriad of diseases (Table). In general, it is estimated that 4% to 7% of all patients diagnosed with AMI, however, do not have CAD at coronary angiography or autopsy.

Another important category that falls within this realm is coronary artery embolism (CE) in which a thrombus arising from sources other than the coronary vasculature propagates into the coronary arteries causing AMI. Previous work on this subject is limited by the small numbers of patients examined, and, given the vast distribution of patients presenting with AMI worldwide, a more systematic approach would greatly improve our understanding of its diverse etiologies, in particular, the role of CE.

In this issue of Circulation, Shibata et al† report on 1776 consecutive cases of new-onset AMI between 2001 and 2013 that were screened for etiology with a focus on CE and a diagnosis based on histological, angiographic, and other diagnostic imaging modalities. Overall, 52 patients were identified with CE, with a prevalence of 2.9%, defined as probable in 20 cases, and definite in 32. The authors implicate atrial fibrillation (AF) as the most common cause of CE, 38 of 52 (73%) patients in comparison with non–AF-related CE, 116 of 1724 (7%) patients (P<0.001). Other etiologies included cardiomyopathy (n=13, 25%) and valvular heart disease (n=8, 15%). The most common causes of AF were chronic AF (25 [66%]) and paroxysmal AF (13 [34%]). CE patients had a lower prevalence of hypertension, diabetes mellitus, dyslipidemia, and smoking, and a lower number of major risk factors for CAD than non-CE AMI patients. Over half of the CE patients (18/30) with nonvalvular AF had CHADS2 scores of 0 or 1, although after reassessment, and with the use of the modified CHA2DS2-VASc criteria, 61% were reassigned to a higher-risk category. Recurrent thromboembolic episodes were identified in 10.4% of patients during follow-up (49 months) and were therefore more likely to benefit from treatment with vitamin K antagonists.

Long-term outcomes between the CE and non-CE cohorts by Kaplan-Meier analysis showed a significantly higher incidence of all-cause death (hazard ratio, 3.82; 95% confidence interval, 2.06–6.48; P<0.001) and cardiac death (hazard ratio, 5.39; 95% confidence interval, 2.38–10.6; P<0.001) in the CE group relative to the non-CE group. The 5-year rates of all-cause death and cardiac death in patients with CE were also significantly higher than those with non-CE (28% versus 7.6%; P<0.001; 17.5% versus 3.4%, P<0.001, respectively). Long-term outcomes indicate that CE patients represent a high-risk subpopulation of patients with AMI and, therefore, will require close follow-up.

Previous studies have linked MI in the absence of underlying CAD to CE. Overall, coronary thrombosis in young patients (≤50 years) may arise from coronary artery aneurysms or from other structural entities such as patent foramen ovale or arterial septal defects. On the other hand, AF is among those disorders contributing to nonatherosclerotic ischemic heart disease, which usually affects patients ≥50 years, particularly individuals in the seventh decade and older. AF is a common clinical problem where age is becoming an established risk factor with an estimated incidence of 9% in those ≥80 years of age. Until recently, AF was more commonly linked to embolic disease causing cerebral infarction, because it is independently associated with a 5-fold increase in stroke. Cerebral thromboembolism by far has been the most important recognized complication of AF and is the most common factor in stroke in the elderly.

A bidirectional causal relationship between AF and MI has recently been proposed by Soliman and collaborators. The authors outlined different scenarios to elucidate this bidirectionality, to include the presence of similar risk factors and higher levels of inflammatory markers, because AF promotes inflammation and a prothrombotic state (AF-induced inflammation), which concurrently can increase the risk of MI. Coronary thromboembolism with subsequent MI has been considered a possible explanation for the observed increased MI risk in patients with AF. Alternatively, episodes of poorly controlled fast AF with an uncontrolled ventricular response...
A prospective cohort study from the Reasons for Geographic and Racial Differences in Stroke (REGARDS)\(^{8}\) concluded that AF was associated with an \( \approx 2 \)-fold increased risk of MI, an association that remained significant after additional adjustments for recognized coronary heart disease risk factors. The risk of MI associated with AF was significantly higher in women than in men and in black participants than in whites with no significant differences in an older population (\( \geq 75 \) years) in comparison with a younger population (\( < 75 \) years).

Although thromboembolism in the absence of CAD is reported as an infrequent cause of AMI, the consequences are potentially life threatening. Distal embolization is clinically recognized by coronary angiography as small peripheral stops, which are otherwise indicators of poor prognosis.\(^{9}\) The overall incidence and prevalence of nonatherosclerotic embolic events resulting in myocardial ischemia and infarction remains unknown, because, for the most part, embolic infarcts are clinically underrecognized.

One of the most detailed autopsy studies of embolic infarcts published in the late 1970s reported the occurrence in 55 of 419 patients (13%), with predisposing conditions of valvular heart disease (40%), cardiomyopathy (29%), coronary atherosclerosis (16%), and chronic AF (24%).\(^{10}\) Complicating the clinical diagnosis of coronary embolism is its distal proximity and potential for recanalization, such that coronary emboli may cause infarcts in territories supplied by angiographically normal coronary arteries. Thus, coronary emboli may not be as rare and may present with signs and symptoms indistinguishable from CAD. Furthermore, thromboemboli tend to lodge distally in typically normal coronary arteries that are becoming intramyocardial, causing small, but transmural myocardial infarcts, which is likely due to poor collateral development in humans without preexisting coronary disease.\(^{10}\)

The limited reported incidence of coronary artery emboli, particularly in nonatherosclerotic CAD, may result from several levels of protection provided by the swift current flow around the coronary ostia, and caliber differences between the aorta and the coronary arteries, and the acute angle at which the coronary arteries originate from the aorta.\(^{11}\) The position of the coronary ostia behind the valve cusp during systole may also guard the coronary arteries from the central stream of the systolic blood flow. Not only are the coronary arteries relatively protected from emboli, in comparison with other organs, but the frequency of multiple emboli from the left atrial appendage also appears lower, as in the current study, which was documented in 8 of 32 (25%) patients with AF-associated CE. It is therefore likely that CEs are underdiagnosed for reasons including a failure to distinguish embolism from thrombosis, underreporting limited to only the most dramatic cases, or a failure to make a systematic search for small emboli in the distal and intramural branches of coronary arteries.\(^{12}\)

The left arterial appendage is an important cardiac structure with embryological, anatomic, and functional differences in reference to the left atrium. Most intracardiac thrombi originate in the left arterial appendage during and after AF.\(^{13}\) Taking into account the clinical profile of subjects with non-valvular AF, a majority of patients will require anticoagulation therapy to prevent thromboembolic complications, and, in recent decades, vitamin K antagonists have been used for this purpose.\(^{14}\) Although warfarin anticoagulation also limits embolic events, there are side effects of bleeding, especially in elderly patients, and it is therefore prescribed in only \( \approx 50\% \) of patients who could benefit medically.\(^{15}\) Moreover, many patients have issues with maintaining a therapeutic level of anticoagulation. Indeed, in the present study, of the 38 AF patients in the CE group, only 15 (39%) were treated with a vitamin K antagonist and their median international normalized ratio was 1.42.

Newer novel oral anticoagulants that inhibit thrombin or activated factor X are also becoming available.\(^{16}\) These agents have the advantage of the lack of dose adjustment and steady-state levels of therapeutic anticoagulation. Expectations in these cases, however, would be that anticoagulation required to reduce the risk of stroke and systemic embolism would also have a significant impact in reducing the thromboemboli that could potentially cause AMI.\(^{17}\) Alternatively, percutaneous left arterial appendage exclusion is also now a clinical reality, and may eventually replace anticoagulant therapy while simultaneously reducing stroke risk.\(^{18}\) The latter treatment, however, in particular, is an invasive procedure in its infancy and will require more study.

The mechanism of AF-related thromboembolism is predicated on the Virchow triad of endothelial damage, hypercoagulable state, and blood stasis, which ultimately results in thrombus formation.\(^{19}\) Left atrial thrombi naturally consist of red blood cells and fibrin, which is typical of low-flow venous conditions and is consistent with the recommendation of oral anticoagulants over antiplatelet drugs for stroke prevention in AF patients.\(^{20}\) Histological examination of the aspirated samples in the study by Shibata et al showed fresh red thrombus without evidence of an atherosclerotic component and in the 28 of 29 AF patients in the CE group that underwent percutaneous coronary intervention. The finding of red thrombi may also have clinical relevance based on the analysis of thrombus aspirates in primary percutaneous coronary intervention in ST-segment–elevation myocardial infarction demonstrating that red thrombi generally have a larger thrombus volume and are associated with an increased

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### Table. List of Reported Causes of Myocardial Infarction From Coronary Embolism in the Absence of Coronary Atherosclerotic Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cardiomyopathy</td>
<td></td>
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<td>Rheumatic heart disease with mitral stenosis</td>
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<tr>
<td>Left ventricular aneurysm</td>
<td></td>
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<tr>
<td>Iatrogenic – injection of thrombus during coronary arteriography</td>
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<tr>
<td>Infectious endocarditis</td>
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<tr>
<td>Marantic endocarditis</td>
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<tr>
<td>Thromboemboli from prosthetic valve</td>
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<tr>
<td>Fibromyxoma of the aortic valve</td>
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<tr>
<td>Atrial myxoma</td>
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Modified from Cheitlin and Virmani.\(^{2}\)
30-day mortality and trend toward lower rates of major adverse coronary events relative to white thrombi mainly consisting of fibrin and platelets.\textsuperscript{21} In this case, a red thrombus constituency developing from AF may be more deleterious in the setting of AMI.

In concordance with the present investigation the relationship of thromboembolism in AF and the caliber of vessel size is not entirely clear. Microvascular obstruction in acute coronary thrombosis and sudden coronary death in an autopsy study of 44 hearts with ruptures and erosions showed that microemboli and microvascular obstruction were common in acute thrombosis.\textsuperscript{22} Plaque erosions were more likely to cause emboli in intramyocardial vessels <200 μm, and were often associated with myocardial necrosis. Overall, 89% of affected microvessels were <120 μm in diameter. Unlike autopsy studies, the size of microvessels involved with AF-associated thromboembolism in AMI in the study by Shibata et al showed involvement of distal epicardial arteries unlike those reported in patients with CAD. The suspected larger volume naturally attributed to red thromboemboli from AF would expect the involvement of even larger-caliber vessels than those originating from CAD.

Estimates concur that ≈2% of individuals in the general population have AF\textsuperscript{23} with the anticipation that numbers will increase substantially in future decades with predictions of greater life expectancy. This news is particularly disturbing, because the rates of CAD-related plaque rupture are generally on the decline in the sixth and seventh decade at a time when the incidence in embolic AMI in the absence of CAD will likely increase. The consequence(s) of the increased prevalence and frequency of AF will ultimately depend on the effectiveness of AF detection and the implementation of preventative measures with anticoagulants, in addition to more extreme measures involving surgical/interventional pulmonary vein isolation through electric ablation and mechanical occlusion. It is becoming more evident that further research is needed to investigate what factors may be contributing to the increasing trends in AF incidence and prevalence and, in particular, its role in AMI in the absence of coronary disease.

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References


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