Embolic Myocardial Infarction as a Consequence of Atrial Fibrillation:

A Prevailing Disease of the Future

Running title: Kolodgie et al.; Embolic Myocardial Infarction

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Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. When spontaneous AMI occurs, there is a greater than 90% chance that the underlying etiology is primary due to coronary events such as plaque rupture, erosion, or dissection referred to as MI Type I \(^1\). Myocardial infarction 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/or demand termed type 2 MI, which embodies a myriad of diseases (Table 1). 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 \(^2\).

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 coronaries causing AMI. Prior 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 1,776 consecutive cases of new onset AMI between 2001 and 2013 that were screened for etiology with a focus on CE and diagnosis based on histological, angiographic, and other diagnostic imaging modalities \(^3\). 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%) as compared to non-AF related CE 116 of 1724 (7%) (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, 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 non-valvular AF had CHADS2 scores of 0 or 1, although after re-assessment and using 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 showed a significantly higher incidence of all-cause death (hazard ratio [HR], 3.82; 95% confidence interval [CI], 2.06 to 6.48; p<0.001) and cardiac death (HR, 5.39; 95% CI, 2.38 to 10.6; p<0.001) in CE group relative to the non-CE. The five-year rates of all-cause death and cardiac death in patients with CE were also significantly higher than those with non-CE (28% vs. 7.6%, p<0.001; 17.5% vs. 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 myocardial infarction in the absence of underlying CAD to CE. Overall, coronary thrombosis in young patients (≤50 years) may arise from coronary artery aneurysms, or other structural entities such as patent foramen ovale (PFO) or arterial septal defects (ASD). 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 7th 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 aged ≥80 years4. Until recently, AF was more commonly linked to embolic disease causing cerebral infarction, as it is independently associated with a 5-fold increase in stroke5. Cerebral thromboembolism by far has been the most important recognized complication of AF, and is the most common factor in stroke in the elderly6.
A bidirectional causal relationship between AF and MI has been 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 since 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 may result in type 2 MI demand infarction, which typically occurs without ST elevation.

A prospective cohort study from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) concluded that AF was associated with an approximate 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 older (≥75 years) compared to 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. The overall incidence and prevalence of “non-atherosclerotic” embolic events resulting in myocardial ischemia and infarction remains unknown, as for the most part, embolic infarcts are clinically under recognized.

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 atrial fibrillation (24%)\(^9\). 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. Further, 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 pre-existing coronary disease\(^9\).

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/or caliber differences between the aorta and the coronary arteries, and the acute angle at which the coronary artery originate from the aorta\(^10\). 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, compared with other organs, but the frequency of multiple emboli from the left atrial appendage also appears lower, as in current study, which was documented in 8 of 32 (25%) patients with AF associated CE. It is therefore, likely that CE are under-diagnosed, for reasons including a failure to distinguish embolism from thrombosis, under-reporting 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\(^11\).

The left arterial appendage (LAA) is an important cardiac structure with embryologic, anatomic, and functional differences in reference to the left atrium (LA). Most intracardiac thrombi originate in the LAA during and after AF\(^12\). 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. Although warfarin anticoagulation also limits embolic events, there are side effects of bleeding, especially in the elderly and is therefore prescribed in only about 50% of patients who could benefit medically. 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 (VKA) and their median INR was 1.42.

Newer novel oral anticoagulants (NOACs) that inhibit thrombin or activated factor X (fXa) are also becoming available. These agents have the advantage of lack of dose adjustment and steady state levels of therapeutic anti-coagulation. 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. Alternatively, percutaneous LAA exclusion are also now a clinical reality, and may eventually replace anticoagulant therapy while simultaneously reducing stroke risk. 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. 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 anti-platelet drugs for stroke prevention in AF patients. Histologic examination of the aspirated samples in the study by Shibata et al showed fresh red thrombus
without evidence of an atherosclerotic component and of the 28 of 29 AF patients in the CE
group that underwent PCI. The finding of red thrombi may also have clinical relevance based on
the analysis of thrombus aspirates in primary PCI in ST-segment elevation myocardial infarction
(STEMI) demonstrating that red thrombi generally have a larger thrombus volume and were
associated with an increased 30-day mortality and trend towards less MACE rates relative to
white thrombi mainly consisting of fibrin and platelets. 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 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 was common acute
thrombosis. Plaque erosions were more likely to cause emboli in intramyocardial vessels
<200μm, and were often associated with myocardial necrosis. Overall, 89% of affected
microvessels were <120μm 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 from those originating from CAD.

Estimates concur that approximately 2% of individuals in the general population have AF
with the anticipation that numbers will increase substantially in future decades with
predictions of greater life expectancy. This news is particularly disturbing, as rates of CAD-
related plaque rupture are generally on the decline in the 6th and 7th decade at a time where 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 implementation of preventative measures with anticoagulants, in addition to more extreme measures involving surgical/interventional pulmonary vein isolation thru electrical ablation and/or mechanical occlusion. It’s 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 particularly its role in AMI in the absence of coronary disease.

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References:


**Table 1.** List of reported causes of myocardial infarction from coronary embolism in the absence of coronary atherosclerotic disease

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
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<tbody>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Rheumatic heart disease with mitral stenosis</td>
</tr>
<tr>
<td>Left ventricular aneurysm</td>
</tr>
<tr>
<td>Iatrogenic – injection of thrombus during coronary arteriography</td>
</tr>
<tr>
<td>Infectious endocarditis</td>
</tr>
<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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</tbody>
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