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REVIEW

The interplay between atrial fibrillation and acute myocardial infarction

Mohamed El-Shetry[1]

Ragab Mahfouz[1]

Abdel-Fattah Frere[1]

Mohamed Abdeldayem[1]

Author details can be found at the end of this article

Correspondence to:
Mohamed El-Shetry;
melshetry@medicine.zu.edu.eg

Abstract

Atrial fibrillation is the most frequently occurring supraventricular arrhythmia in patients presenting with acute myocardial infarction. It is associated with worse outcomes when it coexists with acute myocardial infarction and results in increased morbidity and mortality. Both conditions are closely related to each other and share similar pathophysiological pathways. The management of atrial fibrillation in patients with acute myocardial infarction is challenging since triple antithrombotic therapy is indicated, but this results in a markedly increased risk of bleeding events and mortality. This review addresses the interactions between both conditions including common risk factors, possible mechanisms through which acute myocardial infarction contributes to development of atrial fibrillation and vice versa, and the problem of using anticoagulation in the management of these patients.

Key words: Acute myocardial infarction, Atrial fibrillation, Triple antithrombotic therapy

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Introduction

Atrial fibrillation is not uncommon in the general population and is associated with a major deterioration in quality of life and increased cardiovascular morbidity and mortality. Atrial fibrillation and coronary artery disease can coexist: 17–47% of patients with atrial fibrillation also have coronary artery disease and 1–5% of patients with coronary artery disease also have atrial fibrillation (Michniewicz et al, 2018). Whether new-onset or pre-existing, atrial fibrillation is associated with a worse prognosis and increased mortality in patients presenting with acute myocardial infarction (Shanmugasundaram et al, 2020). Atrial fibrillation is closely related to acute myocardial infarction since they share similar risk factors that increase the frequency of their coexistence. In addition, the co-occurrence of both conditions requires triple antithrombotic therapy that increases the risk of bleeding in those patients. This article summarises possible pathophysiological interactions between these conditions.

Incidence

Acute myocardial infarction is commonly associated with atrial fibrillation: between 6 and 21% of patients presenting with acute myocardial infarction also have atrial fibrillation (Schmitt et al, 2009).

Prognostic implications

Atrial fibrillation occurs frequently in patients with ST-segment elevation myocardial infarction and is associated with increased re-infarction rates, cardiogenic shock and pulmonary oedema. It is also an independent predictor of both short- and long-term mortality in patients with acute myocardial infarction. The specific mechanism of increased mortality in patients with both atrial fibrillation and acute myocardial infarction is still unclear, but it has been suggested that atrial fibrillation is common in older people with more comorbidities that could carry additional mortality risk (Shanmugasundaram et al, 2020).

Risk factors

In the Atherosclerosis Risk In Communities (ARIC) study (Soliman et al, 2015), atrial fibrillation was found to be associated with nearly 63% increased risk of acute myocardial

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infarction. Several cardiovascular risk factors can promote development of both conditions; these risk factors are summarised in Table 1 and discussed in the following sections.

Ageing

The Framingham Heart Study demonstrated that age is the most important risk factor for the development of atrial fibrillation (Schnabel et al, 2015). The exact pathophysiological mechanism of how ageing predisposes to atrial fibrillation is not fully understood. Cardiomyocytes decrease in number during a person's lifetime and are partially replaced by fibrotic tissue, which leads to alterations in cellular conductivity and variable arrhythmogenic responses. Another possible explanation is the reduction in sinoatrial node discharge and simultaneously enhanced impulse generation from ageing atrial cells located within the coronary sinus and pulmonary veins. Similarly, the prevalence of myocardial infarction increases with ageing. The prevalence of acute myocardial infarction in people over 80 years of age is about five times greater than that in individuals between 40 and 60 years of age (Mozaffarian et al, 2016).

Hypertension

Pathophysiologically, hypertension results in atrial dilation and dysfunction, in addition to left ventricular hypertrophy and diastolic dysfunction, increasing the risk of developing atrial fibrillation. Left ventricular hypertrophy and activation of the renin–angiotensin–aldosterone system are linked to an increased risk of acute myocardial infarction (Toh et al, 2010).

Obesity

The role of obesity in the development of both atrial fibrillation and acute myocardial infarction has been well established. Abdominal fat plays a critical role in the pathogenesis

Table 1. Risk factors for both atrial fibrillation and acute myocardial infarction

Risk factors	Atrial fibrillation	Acute myocardial infarction
Ageing	Decreased number of cardiomyocytes, decreased sinoatrial node discharge	Increased prevalence of acute myocardial infarction with ageing
Hypertension	Atrial dilatation and dysfunction Left ventricular hypertrophy and diastolic dysfunction	Left ventricular hypertrophy and renin–angiotensin–aldosterone system activation
Obesity	Increased cardiac output and left ventricular hypertrophy leads to diastolic dysfunction and increased left atrial pressure, increased body mass index increases the incidence of atrial fibrillation, pericardial fat releases inflammatory mediators, eg tumour necrosis factor-α, interleukin-6	Abdominal fat plays a critical role in its pathogenesis and predicts mortality
Diabetes	Deposition of advanced glycation endproducts leads to increased left ventricular stiffness	Deposition of advanced glycation endproducts leads to dysfunction of the coronary microcirculation
Smoking	Enhanced sympathetic activity Upregulation of transforming growth factor-β1 leads to atrial structural remodelling	Systemic inflammation and endothelial dysfunction lead to atherogenesis, aggravation of dyslipidaemia and insulin resistance
Dyslipidaemia	Lower levels of low-density lipoprotein and total cholesterol lead to increased risk of atrial fibrillation	Increased levels of low-density lipoprotein and lower levels of high-density lipoprotein lead to increased risk of atrial fibrillation
Alcohol intake	Even low levels of alcohol intake lead to increased risk of atrial fibrillation	Moderate alcohol consumption leads to increased levels of high-density lipoprotein and adiponectin, decreased levels of fibrinogen has a protective effect
Sleep-disordered breathing	Intermittent apnoea and arousal lead to activation of the sympathetic nervous system, which leads to increased blood pressure, heart rate and systemic inflammation, which leads to increased risk of atrial fibrillation and acute myocardial infarction	

of acute myocardial infarction and is an independent predictor of all-cause mortality (Kragelund et al, 2005). The risk of developing atrial fibrillation increases with increasing body mass index. A meta-analysis of 51 studies demonstrated that an increase of body mass index about 5 kg/m^2 is associated with 29% greater risk of atrial fibrillation (Wong et al, 2015). Interestingly, mildly obese patients and those who are overweight have a better prognosis than normal weight individuals. This 'obesity paradox' applies to most cardiovascular diseases, including atrial fibrillation and acute myocardial infarction (Zhu et al, 2016). Possible mechanisms through which obesity increases the risk of atrial fibrillation, acute myocardial infarction and their co-occurrence include haemodynamic changes caused by increased cardiac output and left ventricular hypertrophy resulting in diastolic dysfunction and increased left atrial pressure. Furthermore, pericardial fat (a highly biologically active component) appears to have a major role in development of atrial fibrillation, mediated through local inflammatory effects on atrial tissue and subsequent fibrosis. Pericardial fat releases inflammatory mediators, including tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which have direct arrhythmogenic effects on atrial tissue and increase the risk of developing atrial fibrillation (Tereshchenko et al, 2014).

Diabetes

Diabetes is usually associated with increased cardiovascular morbidity and mortality rate in patients having atrial fibrillation and acute myocardial infarction. Pathophysiological pathways of cardiac impairment in diabetic patients include deposition of advanced glycation end-products resulting in increased left ventricular stiffness, coronary microcirculation dysfunction and autonomic neuropathy. These changes result in structural remodelling of the atria, providing a potential trigger for the development of atrial fibrillation. Advanced glycation end-products and high levels of reactive oxygen species usually play a role in these changes. Furthermore, diabetes causes increased sympathetic and decreased parasympathetic cardiac activity, making patients with acute myocardial infarction more vulnerable to atrial fibrillation (Saito et al, 2014).

Smoking

Smoking also increases the risk of atrial fibrillation and acute myocardial infarction. Postulated pathophysiological mechanisms include enhanced sympathetic neurotransmission and catecholamine release. Additionally, nicotine causes atrial structural remodelling through upregulation of transforming growth factor (TGF)-β1, thus providing a pro-arrhythmogenic substrate for development of atrial fibrillation. Smoking also contributes to the development of coronary artery disease through proatherogenic effects including systemic inflammation and endothelial dysfunction, in addition to aggravation of dyslipidaemia and insulin resistance (Bye et al, 2008).

Dyslipidaemia

Acute myocardial infarction is associated with high levels of low-density lipoprotein and low levels of high-density lipoprotein cholesterol. As a result, lipid-lowering drugs have been widely used for primary and secondary prevention of acute myocardial infarction. Paradoxically, an inverse relation between low levels of total cholesterol and low levels of low-density lipoprotein cholesterol and atrial fibrillation has been described (Mourtzinis et al, 2018), although the exact pathophysiology beyond this paradoxical association remains unclear.

Alcohol consumption

Alcohol intake, even at low levels, increases the risk of developing atrial fibrillation. On the other hand, moderate alcohol consumption has a protective effect for the occurrence of acute myocardial infarction, and low levels of alcohol intake is associated with decreased mortality rates after acute myocardial infarction. Suggested markers of lower incidence of acute myocardial infarction and decreased mortality include changes in cardiovascular biomarkers: increased levels of high-density lipoprotein and adiponectin and decreased levels of fibrinogen (Brien et al, 2011).

Breathing problems

Sleep-disordered breathing and obstructive sleep apnoea can contribute to the development of atrial fibrillation and acute myocardial infarction. Previous studies found that obstructive sleep apnoea is prevalent in patients with atrial fibrillation compared to those without (21–74% vs 3–49%). Obstructive sleep apnoea mostly predisposes to atrial fibrillation and acute myocardial infarction directly through intermittent episodes of apnoea and arousal which result in activation of sympathetic nervous system, increased blood pressure and heart rate, increased negative intrathoracic pressure, ischaemia and systemic inflammation (Marulanda-Londono and Chaturvedi, 2017).

Interplay between atrial fibrillation and acute myocardial infarction

There are multiple pathophysiological interactions between atrial fibrillation and myocardial infarction.

Atrial fibrillation as a possible cause of acute myocardial infarction

There are multiple possible explanations of how atrial fibrillation can contribute to the development of acute myocardial infarction. These include:

Inflammation

Atrial fibrillation promotes systemic inflammation and endothelial dysfunction, thus leading to the development of coronary artery disease and myocardial infarction. High levels of biomarkers of inflammation and haemostasis were found to be associated with atrial fibrillation and coronary artery disease (Zakynthinos and Pappa, 2009). Patients with atrial fibrillation who have increased levels of D-dimer have an increased risk of stroke and coronary artery disease. High circulating levels of C-reactive protein are also associated with an increased risk of stroke, vascular events and mortality in patients with atrial fibrillation. Systemic inflammation may result from atrial fibrillation alone or from the associated classical atherosclerotic risk factors which are commonly associated with atrial fibrillation (Violi et al, 2016).

Platelet activation

Several biomarkers of platelet activation including P-selectin, β-thromboglobulin, soluble CD40L (sCD40L), and prostaglandin F2-alpha (PGF2-α) were found to be elevated in patients with atrial fibrillation, suggesting a potential role of platelets in development of vascular disease and occurrence of cardiac complications (Pignatelli et al, 2015).

Tachycardia

Uncontrolled attacks of tachycardia in patients with atrial fibrillation result in increased myocardial oxygen demand and decreased coronary blood flow, predisposing to type 2 myocardial infarction (demand–supply mismatch). Both increased oxygen consumption and decreased diastolic duration; during which coronary blood flow occurs, predisposing to development of acute myocardial ischaemia in the presence of associated coronary artery disease (Camici et al, 2016).

Vasomotor impairment

Vasomotor impairment is widespread as a result of associated endothelial dysfunction, and causes reduction in coronary blood flow following active vasoconstriction. On the other hand, atrial stretch acutely enhances sympathetic activity, and stimulates release of catecholamines from the heart resulting in coronary vasoconstriction through stimulation of alpha-adrenergic receptors (Millar et al, 2013).

Coronary thromboembolism

Coronary thromboembolism mostly results in sudden, complete occlusion of coronary arteries, and thus is expected to result in ST-segment elevation myocardial infarction. However, the contribution of atrial fibrillation to acute myocardial infarction was only confirmed for non-ST-segment elevation myocardial infarction in the ARIC study, indicating

that coronary thromboembolism is a rare cause of acute myocardial infarction in patients with atrial fibrillation (Soliman et al, 2015).

Acute myocardial infarction as a possible cause of atrial fibrillation

Coronary artery disease affecting the atrial branches of the circumflex and coronary arteries (specifically the left circumflex atrial branch, sinoatrial branch, right atrial intermediate branch and atrionodal branch) strongly predicts the development of atrial fibrillation after acute myocardial infarction (Alasady et al, 2011). Postulated mechanisms of atrial fibrillation complicating acute myocardial infarction include the following:

Atrial infarction

Experimentally, it was found that marked reduction of blood flow in the right and left circumflex coronary artery branches that perfuse the atria results in increased excitability of atrial cardiomyocytes and decreased conduction velocity, precipitating re-entry mechanisms and atrial fibrillation. Abnormal P wave morphology (Liu minor criteria) was also found to significantly predict new-onset atrial fibrillation in patients with atrial infarction (van Diepen et al, 2010).

Atrial overstretch

Atrial overstretch from high atrial pressure as a result of atrial ischaemia or left ventricular dysfunction increases excitability of atrial cardiomyocytes and the length of the conduction pathway, again favouring re-entry mechanisms and atrial fibrillation. Chronic ischaemia and the resultant atrial fibrosis also promote re-entry mechanisms. Atrial stretch also leads to atrial fibrillation through an effect on atrial refractoriness. Previous studies revealed that left atrial enlargement is an independent predictor for new-onset atrial fibrillation after acute coronary syndromes. Presumably, factors decreasing atrial pressure could decrease the incidence of atrial fibrillation after acute coronary syndromes. It has been suggested that angiotensin-converting enzyme inhibitor therapy can decrease the risk of atrial fibrillation by decreasing atrial pressure and minimising left atrial enlargement (Wang et al, 2015).

Inflammation

Inflammation also plays an important role in initiation and maintenance of atrial fibrillation. During acute myocardial infarction, cytokines are released by immune, vascular and interstitial tissues for regulating important biological processes of cell growth, migration, repair and fibrosis. Cytokine expression is also upregulated in the non-infarcted or non-ischaemic areas of the myocardium. Thus, the development of atrial fibrillation in patients with acute myocardial infarction could be a sign of extensive inflammation. Given the important role of the inflammatory reaction in the development of atrial fibrillation, anti-inflammatory drugs could decrease the incidence of this arrhythmia in the setting of acute myocardial infarction. There is evidence that early statin therapy is associated with lower incidence of atrial fibrillation, regardless of the type and dose of statin given. Statins have pleiotropic effects, including preservation of endothelial function, anti-inflammatory effects, and antioxidant properties in addition to their lipid-lowering properties. These effects provide the basis for assuming that statins may lower the risk of developing atrial fibrillation, but the exact mechanisms are still not completely understood (Adam et al, 2008).

Nervous systems

Both sympathetic and parasympathetic nervous systems also play an important role in the development of atrial fibrillation. The expression of low vagal tone and increased sympathetic output was demonstrated after acute myocardial infarction. Thus, blocking sympathetic activation with β-adrenoreceptor blockers could reduce the incidence of new-onset atrial fibrillation after acute myocardial infarction through synergistic actions as anti-adrenergic, anti-ischaemic, and anti-arrhythmic agents (De Mattia et al, 2012).

Hormones

Hormonal activation also plays an important role in the development of atrial fibrillation in the setting of acute myocardial infarction. Elevated levels of B-type natriuretic peptide,

released from the ventricles as a result of elevated left ventricular pressure and volume, can predict the development of atrial fibrillation in patients with acute myocardial infarction (Parashar et al, 2010).

Subclinical hyperthyroidism was found to be associated with paroxysmal atrial fibrillation during acute myocardial infarction. Subclinical hyperthyroidism (decreased thyroid-stimulating hormone level with normal serum free thyroxine and free triiodothyronine levels) can induce arrhythmias including atrial fibrillation (Patanè and Marte, 2010).

Oestrogen replacement therapy was found to lower the risk of development of atrial fibrillation in women with acute myocardial infarction. Possible mechanisms for this include the anti-inflammatory effect of oestrogen and its effects on ischaemic preconditioning, cardiomyocyte apoptosis and neovascularisation (Karim et al, 2010).

The challenge of anticoagulation in these patients

Patients with atrial fibrillation have increased thromboembolic risk as a result of activation of the coagulation system rather than as a result of platelet activation, therefore anticoagulants affecting the coagulation cascade are more effective than antiplatelet agents in preventing thromboembolic events. In patients with atrial fibrillation, thrombi develop mainly in the left atrial appendage, and are characterised by low shear stress with less dominant platelet component (Simmers et al, 2016). On the other hand, localised endothelial damage in the coronary arteries is the main mechanism precipitating thrombosis in patients with acute myocardial infarction and mainly arises from atherosclerotic plaque rupture exposing thrombogenic material in the plaque core to circulating blood, stimulating platelet aggregation and the formation of a platelet-rich thrombus. Hence, antiplatelet agents are the cornerstone of treatment in patients with acute myocardial infarction (Goto et al, 2008).

The latest European Society of Cardiology guidelines recommend assessment of stroke risk and bleeding risk before initiating anticoagulant therapy. Common stroke risk factors are summarised in the CHA2DS2-VASc score (Congestive Heart failure [1 point], hypertension [1 point], Age ≥75 years [2 points], Diabetes [1 point], Stroke [2 points], Vascular disease [1 point], Age 65 to 74 years [1 point] and female Sex [1 point]). Patients at low stroke risk (CHA2DS2-VASc score=0 in men, or 1 in women) do not require antithrombotic therapy, those with score ≥2 in men or ≥3 in women should receive oral anticoagulant therapy (class I, level of evidence A) and those with a score of 1 in men or 2 in women should have an individualised decision regarding oral anticoagulant therapy based on the net clinical benefit and patient preference (class IIa, level of evidence B) (Hindricks et al, 2020).

On the other hand, risk assessment using the HAS-BLED score should be considered to identify patients at high risk of bleeding (HAS-BLED score ≥3) who need early and more frequent monitoring and follow up. Clinical risk factors in the HAS-BLED score include uncontrolled Hypertension (systolic blood pressure >160 mmHg) [1 point], Abnormal renal and/or hepatic function [1 point for each], Stroke [1 point], Bleeding history or predisposition [1 point], Labile INR [1 point], Elderly >65 years [1 point], Drugs or excessive alcohol drinking [1 point for each] (Hindricks et al, 2020).

It is worth noting that a direct oral anticoagulant is recommended over warfarin in all eligible patients, unless they have moderate to severe mitral stenosis or a mechanical prosthetic heart valve (class I, level of evidence A). In patients at high risk of bleeding (HAS-BLED ≥3), rivaroxaban 15 mg once daily and dabigatran 110 mg twice daily are preferred to rivaroxaban 20 mg once daily and dabigatran 150 mg twice daily respectively for the duration of concomitant single or dual antiplatelet therapy, to minimise the bleeding risk. On the other hand, when a vitamin K antagonist is indicated, target international normalised ratio should be reduced to 2–2.5 (class IIa, level of evidence B). In patients with atrial fibrillation in whom oral anticoagulant therapy is contraindicated, left atrial appendage occlusion may be considered (class IIb, level of evidence B). Surgical occlusion of the left atrial appendage may also be considered in patients with atrial fibrillation who are undergoing cardiac surgery (class IIb, level of evidence C) (Hindricks et al, 2020).

In the setting of acute myocardial infarction, patients with atrial fibrillation who are undergoing uncomplicated percutaneous coronary intervention are recommended to stop

Key points

- Atrial fibrillation is associated with a worse prognosis and increased mortality in patients with acute myocardial infarction.
- Atrial fibrillation can contribute to development of acute myocardial infarction through mechanisms including systemic inflammation, endothelial dysfunction, platelet activation and uncontrolled episodes of tachycardia resulting in demand–supply mismatch.
- Acute myocardial infarction can contribute to development of atrial fibrillation through mechanisms including atrial infarction, atrial overstretch as a result of atrial ischaemia and left ventricular dysfunction, high sympathetic output and systemic inflammation.
- Patients with atrial fibrillation and acute myocardial infarction who have a low risk of stent thrombosis or a high bleeding risk are recommended to stop aspirin early (≤1 week) and continue dual therapy with an oral anticoagulant and clopidogrel for up to 12 months.
- Triple therapy with aspirin, clopidogrel and an oral anticoagulant for longer than 1 week and less than 1 month should be considered for patients with an increased risk of stent thrombosis that outweighs the bleeding risk.

aspirin early (≤1 week) and continue dual therapy with an oral anticoagulant and a P2Y12 inhibitor (clopidogrel is preferred) for up to 12 months if the risk of stent thrombosis is low or if there is a high risk of bleeding (HAS-BLED ≥3). On the other hand, triple therapy with aspirin, clopidogrel and an oral anticoagulant for longer than 1 week and less than 1 month should be considered when there is increased risk of stent thrombosis that outweighs the risk of bleeding (Hindricks et al, 2020).

Conclusions

Atrial fibrillation and acute myocardial infarction are closely related disease entities that often co-exist. Both conditions share similar risk factors and are associated with worse outcomes when they occur together. Patients with atrial fibrillation in the setting of acute myocardial infarction require triple antithrombotic therapy that further increases the risk of bleeding and hence need careful assessment of stroke and bleeding risks.

Author details

[1]Department of Cardiology, Zagazig University, Zagazig, Egypt

Conflict of interest

The authors declare that there is no conflict of interest.

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