Metabolic syndrome and postoperative atrial fibrillation (POAF)

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Online publish-ahead-of-print 17 April 2009

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice, and the lifetime risk of developing AF is 25%. Even in the absence of structural heart disease AF is extremely common and is associated with an increased risk of stroke, heart failure, and death. Risk factors for AF are age, sleep apnoea, valvular heart disease, hypertension, obesity, male gender, and type 2 diabetes.1

The key lesion in developing AF is dilation of the left atrium, for which there are multiple causes in the type 2 diabetic patient.2 Approximately 75% of type 2 diabetic subjects are hypertensive. For every molecule of glucose that is filtered and reabsorbed in the kidney, one molecule of sodium is also absorbed. High insulin and glucose levels lead to salt and water retention, activation of the sympathetic nervous system, activation of angiotensin II receptors, and increased free fatty acid levels. In addition, insulin resistance is associated with increased sodium and calcium content of the vascular smooth muscle cells (VSMCs) and remodelling of the arterial wall due to proliferation of VSMCs.3 Even in the absence of hypertension, left ventricular hypertrophy (LVH) and stiffening and thickening of the arterial wall often develop in the diabetic patient due to the trophic effects of angiotensin, aldosterone, and hyperinsulinaemia. Overall, 71% of type 2 diabetic subjects have LVH, and another 50–60% have diastolic dysfunction due to diabetic cardiomyopathy.4 Thus, for various reasons, including hypertension, LVH, diabetic cardiomyopathy, and heart failure, insulin-resistant and/or type 2 diabetic patients often develop dilation of the left atrium. While ectopic foci in pulmonary veins trigger the development of AF, the persistence of AF is dependent upon atrial fibrosis and electrical and structural remodelling of the left atrium.5

While it is tempting to speculate that hyperglycaemia, leading to formation of advanced glycation end-products and atrial fibrosis, would play a role in the initiation or progression of the structural and electrical remodelling of the atrium, this is unlikely since an increased incidence or prevalence of AF has never been reported in type 1 diabetic subjects. Therefore, the major underlying reason for the increased frequency of AF in the type 2 diabetic patient is likely to be the metabolic syndrome (MetSyn).6

The MetSyn is characterized by increased peritoneal fat, insulin resistance and hyperinsulinaemia, inflammation, oxidative stress, and endothelial dysfunction. Components of the MetSyn include hypertension, and dyslipidaemia which is characterized by a low high-density lipoprotein (HDL) and a high triglyceride level. The non-diabetic patient with MetSyn, like the type 2 diabetic subject, is prone to hypertension and LVH, which results in left atrial dilatation. Left atrial stretch leads to left atrial remodelling which is characterized by loss of muscle mass, fibrosis, dilation, and disruption of cell coupling at gap junctions. While these changes predispose to the development of atrial arrhythmias, once AF develops, rapid atrial rates lead to escalation of the remodelling process (hence the old clinical adage: AF begets AF). A study of new-onset AF showed that subjects with the MetSyn had significantly larger left atrial dimensions than those without MetSyn.3 Furthermore, when corrected for left atrial dilatation, obesity is no longer an independent factor for AF. Therefore, MetSyn leading to atrial dilatation is the major reason for the increased incidence and prevalence of AF in insulin-resistant and/or diabetic patients.

The MetSyn is an inflammatory state which leads to increased levels of adipocytokines such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP),2 as well as free fatty acids,6 which causes vasoconstriction and endothelial dysfunction. The inflammation, oxidative stress, and endothelial dysfunction induced by the MetSyn may lead to atrial damage and structural and electrical remodelling of the atrium.6 Indeed, CRP levels and oxidative stress are increased in subjects with AF.7

Obstructive sleep apnoea (OSA) appears to be one of the strongest risk factors for AF, and is present in ~60% of individuals.
with this dysrhythmia.\textsuperscript{8} Pathological alterations that occur in OSA that may predispose to AF include hypoxaemia, sympathetic activation, hypertensive surges, atrial stretching caused by negative intrathoracic pressure induced by inspiring against a closed glottis, and systemic inflammation. Because OSA is a common and correctable cause of AF, the recognition and treatment of ordered sleep breathing is essential for individuals with or at risk for AF. Most individuals with OSA also have MetSyn. Indeed, due to the very common overlap of these two problems, AF should be considered to be due to OSA until proven otherwise. While OSA has not yet been shown to be an independent risk factor for postoperative atrial fibrillation (POAF), its association with obesity, MetSyn, inflammation, oxidative stress, increased sympathetic activity, and neurohormonal imbalance makes OSA a very likely factor in the aetiology of POAF.

Coronary artery bypass graft (CABG) surgery markedly increases oxidative stress and systemic inflammation. POAF occurs in 25% of patients undergoing CABG, and is associated with increases in mortality, postoperative stroke, hospital stays, and hospital costs. Girerd et al., who had already shown that MetSyn was an independent risk factor for POAF, have now shown that POAF could be predicted by the presence of an increased waist circumference and an elevated CRP level.\textsuperscript{9} The authors suggest that a trial of perioperative anti-inflammatory therapy in patients with these features should be performed.

Which anti-inflammatory agent would be appropriate for use in this trial? Statins, β-blockers, and renin–angiotensin system (RAS) blockers are all logical agents to reduce inflammation, and prior studies indicate that they may be helpful in preventing AF.\textsuperscript{10} Fish oil (omega-3 fatty acids), another anti-inflammatory therapy, reduced the occurrence of AF by ~50% in a small randomized trial.\textsuperscript{11} However, many diabetic patients would and should already be using these agents that have been proven to alter cardiovascular prognosis favourably. On the other hand, a thiazolidinedione (TZD) might be an excellent drug to test in a placebo-controlled double-blind trial to reduce POAF. This class of drugs has been shown significantly to decrease both inflammation and oxidative stress and significantly to improve endothelial function. TZDs have already been shown to decrease restenosis following angioplasty, and their use with bare metal stents has been shown to achieve similar restenosis rates to that obtained with a drug-eluting stent.\textsuperscript{12} These findings are probably due not only to the anti-inflammatory but also to the anti-proliferative effects of TZDs. Case studies of improvement in paroxysmal AF with TZDs have been described, and in a small nested case–control study of diabetic patients, utilizing TZDs achieved a 20% non-significant decrease in POAF.\textsuperscript{13} Unlike RAS inhibitors, β-blockers, and statins, the withdrawal or omission of which would be unethical in many patients who require cardiac surgery, TZDs are ‘optional’ and therefore a reasonable medication to study against placebo, and in non-diabetic subjects would not cause hypoglycaemia.

While a majority of MetSyn subjects are obese, there are those, particularly of Asian origin, who are thin. Measuring the waist circumference in this group could be particularly beneficial in the detection of MetSyn especially when it is compared with height (the waist/height ratio).\textsuperscript{14} However, a better screening tool for MetSyn is the fasting triglyceride to HDL ratio which if in excess of 3.6 has a strong association with MetSyn.\textsuperscript{15}

The evidence that POAF is associated with MetSyn is now well established. The likelihood is that the association is due to the increases in the inflammation and oxidative stress that occur with MetSyn. Clinical trials to assess the possibility of avoiding POAF and its associated negative outcomes by utilizing preoperative anti-inflammatory therapy are needed. Hopefully, prophylactic anti-inflammatory therapies will reduce not only the incidence of POAF but also the incidence of POAF’s consequences.

**Conflict of interest:** J.H.O. is a Consultant and Speaker for GlaxoSmithKline; and a speaker for AstraZeneca, Merck-Schering Plough, and Novartis. D.S.H.B. is a Consultant and Speaker for Bristol Myers-Squibb, Novo Nordisk, Novartis, and Takeda.

**References**