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Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery

M. Zakkar [a], R. Ascione [a], A.F. James [b], G.D. Angelini [a], M.S. Suleiman [a,*]

[a] Bristol Heart Institute, University of Bristol, Level 7, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK
[b] School of Physiology & Pharmacology, University of Bristol, Medical Sciences Building, University Walk, Bristol, BS8 1TD, UK

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ABSTRACT

Postoperative atrial fibrillation (POAF) is a common complication of cardiac surgery that occurs in up to 60% of patients. POAF is associated with increased risk of cardiovascular mortality, stroke and other arrhythmias that can impact on early and long term clinical outcomes and health economics. Many factors such as disease-induced cardiac remodelling, operative trauma, changes in atrial pressure and chemical stimulation and reflex sympathetic/parasympathetic activation have been implicated in the development of POAF. There is mounting evidence to support a major role for inflammation and oxidative stress in the pathogenesis of POAF. Both are consequences of using cardiopulmonary bypass and reperfusion following ischaemic cardioplegic arrest. Subsequently, several anti-inflammatory and antioxidant drugs have been tested in an attempt to reduce the incidence of POAF. However, prevention remains suboptimal and thus far none of the tested drugs has provided sufficient efficacy to be widely introduced in clinical practice. A better understanding of the cellular and molecular mechanisms responsible for the onset and persistence of POAF is needed to develop more effective prediction and interventions.

Contents

1. Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with ensuing deterioration of mechanical function (Potpara & Lip, 2011; Andrade et al., 2014; Weijs et al., 2014). Post-operative AF (POAF) is a common complication (typically occurring within the first 2 to 3 days) after cardiac surgery with an incidence up to 60% depending on the type of surgery (coronary artery bypass graft surgery, valve surgery, or combined) (Maisel et al., 2001; Ascione et al., 2002; Mostafa et al., 2012; Orenes-Pinero et al., 2012; Hernandez-Romero et al., 2014). Patients with POAF have increased risk of cardiovascular mortality, stroke and other arrhythmias than patients without POAF (El-Chami et al., 2010; Mostafa et al., 2012; Brooks & Schindler, 2014; Philip et al., 2014).

Pre-existing co-morbidities, operative trauma, ischaemia and reperfusion injury during surgery, changes in atrial pressure due to postoperative ventricular stunning, chemical stimulation and reflex sympathetic/parasympathetic activation have all been identified as contributing factors (Maisel et al., 2001; Ferro et al., 2009; Maesen et al., 2012; Mostafa et al., 2012). The incidence of POAF differs between

Abbreviations: AF, atrial fibrillation; ATP, adenosine triphosphate; CA, cardioplegic arrest; CPB, cardiopulmonary bypass; CABG, Coronary artery bypass grafting; CRP, C-reactive protein; IL, interleukin; LVH, left ventricle hypertrophy; MAO, monoamine oxidase; MS, metabolic syndrome; mPTP, mitochondrial permeability transition pore; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NRF2, nuclear factor, erythroid 2-like 2; NF-KB, nuclear Factor-KB; n-PUFAs, n-3 polyunsaturated fatty acids; POAF, postoperative atrial fibrillation; ROS, reactive oxygen species; RBC, red blood cells; GSHt, total glutathione; TGF-β1, transforming growth factor-β1; TNF-α, tumour necrosis factor α; VWF, Von Willebrand factor.

* Corresponding author at: School of Clinical Sciences and the Bristol Heart Institute, University of Bristol, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK. Tel.: +44 117 3423519.
E-mail address: m.s.suleiman@bristol.ac.uk (M.S. Suleiman).

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different forms of cardiac surgery, indicating that the pro-arrhythmia depends on processes triggered by the surgical intervention itself (Creswell et al., 1993). However, little is known about the cellular and molecular mechanisms responsible for the onset or perpetuation of POAF. What is known however is that POAF has some pro-arrhythmic mechanisms in common with other forms of AF as supported by data demonstrating that patients who develop POAF have a degree of structural remodelling evident by a larger left atrium, a tendency towards having larger left atrial appendage dimension, and lower left atrial ejection fraction. Additionally, those patients tend to have increased atrial conduit function, and evidence of left ventricular diastolic relaxation impairment compared to those without AF (Aytemir et al., 1999; Nakai et al., 2002; Leung et al., 2004; Ferro et al., 2009; Maesen et al., 2012; Nardi et al., 2012). Other abnormalities that have been associated with increased incidence of POAF include high pre-operative levels of cholesterol (Aydin et al., 2014). Relevant to this is the finding that metabolic syndrome (MS) is an independent predictor of POAF (Brown & Moukdar, 2013; Hurt et al., 2013; Montaigne et al., 2013). MS represents a cluster of metabolic events related to various degrees of insulin resistance such as central obesity and hypertension, thus increased risk of developing type 2 diabetes mellitus. Mitochondrial dysfunction in patients with MS has been linked to the development of arrhythmias (Montaigne et al., 2013), possibly mediated by increased sensitivity to calcium-induced mitochondrial permeability transition pore (mPTP) opening.

Finally, POAF has in recent years been closely linked to pro-inflammatory mediators and oxidative stress. The level of inflammation and oxidative stress is related to the pre-operative status and to the triggers associated with cardiac surgery (Fig. 1). This review will focus on the role of inflammation and oxidative stress in the pathogenesis of POAF and their potential as therapeutic targets.

2. Origins of inflammatory response during open heart surgery

The inflammatory response during cardiac surgery is largely due to the operative trauma involving surgery, CPB and organ reperfusion injury. However, a less known source of inflammatory response is associated pre-operative cardiovascular disease state.

2.1. Inflammatory state prior to surgery

Patients undergoing open heart surgery are likely to have a pre-operative chronic inflammatory state that can be triggered by cardiac disease and co-existing co-morbidities. For example there is a close link between atherosclerosis and inflammation where atherosclerosis is considered an inflammatory disease (Anogeianaki et al., 2011). Furthermore, there is strong experimental evidence to suggest that atherogenic stimuli (e.g., diabetes, dyslipidaemia) do in fact trigger vascular inflammatory response which indirectly contributes to stable atherosclerotic disease and that plaque disruption is triggered by subsequent inflammatory stimuli (Libby & Crea, 2010; Libby, 2012). The source of the inflammatory response is not necessarily systemic as ischaemic disease-induced cardiac remodelling can in principle produce a local inflammatory response as supported by work showing that hypoxic cardiomyocytes produce cytokines (Sawa et al., 1998). One reason for the fact that this chronic disease-related inflammatory response has not received much attention from the scientific community could be the relatively low levels of circulating inflammatory markers. However, this is likely to be more relevant following an acute infarction as has been demonstrated in experimental models (Deten et al., 2002; Deten & Zimmer, 2002). In clinical settings, cytokines including IL6 are acutely elevated during ST- or non-ST-elevation acute coronary syndromes (Neumann et al., 1995; De Servi et al., 2014). Markers of inflammation are also elevated in heart failure which can be reduced by cardiac resynchronization therapy (Rubaj et al., 2013).

2.2. Systemic Inflammatory response during surgery

The main inflammatory response seen during cardiac surgery (both systemic and non-systemic) is associated with the surgery itself. An acute systemic inflammatory response is initiated by a number of injurious processes including surgical trauma, CPB and organ reperfusion injury (Paparella et al., 2002). CPB is a major trigger of inflammatory response during cardiac surgery since off-pump surgery has been shown to significantly reduce inflammatory response (e.g. (Ascione et al., 2000; Caputo et al., 2002; Nesher et al., 2006)). CPB can impact upon the cellular and non-cellular elements of blood resulting in the activation of different pro-inflammatory cascades (Hill, 1998; Anselmi et al., 2004; Khoynezhad et al., 2004; Rinder, 2006; Suleiman et al., 2008). It is now generally accepted that CPB is a direct trigger of cardiac injury since miniaturized cardiopulmonary bypass is associated with less cardiac injury compared to conventional bypass (Remadi et al., 2006; Skrabal et al., 2007; El-Essawi et al., 2010; Nguyen et al., 2014). More importantly, miniaturized cardiopulmonary bypass is associated with less inflammatory response (van Boven et al., 2004; Remadi et al., 2006; Skrabal et al.,

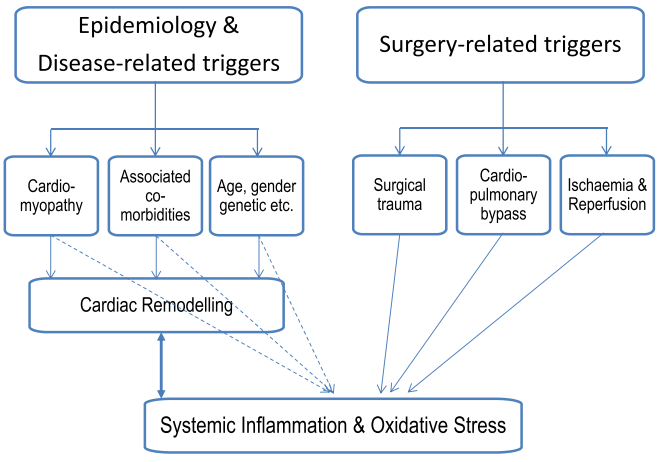

Fig. 1. Flow chart showing the source of inflammation & oxidative stress pre-and postoperatively. See text for details.

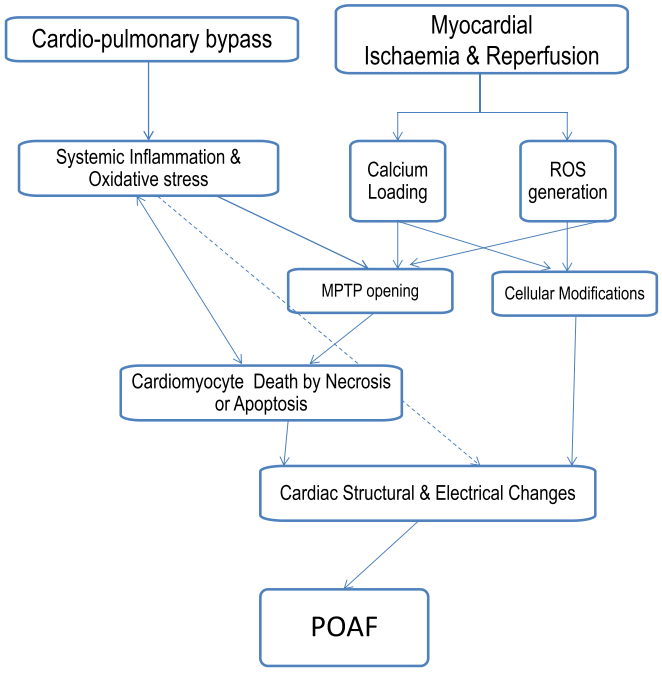

Fig. 2. Flow chart showing the effect of CPB and ischaemia and reperfusion on cardiac remodelling that can lead to POAF.