Introduction

The mechanisms underlying the development of complications associated with cardiac surgery are multifactorial and have been related to inflammation and oxidative stress, classically measured in the blood or plasma of patients. This is important since cardiac surgery alters the integrity of the pericardial membrane and causes significant alterations in the pericardial fluid (PF) composition. This can potentially have adverse effects on the thin-walled atria leading to postoperative atrial fibrillation (POAF). After cardiac surgery, the pericardium remains open, and chest drains are routinely placed to prevent fluid accumulation around the heart. It has been described that the concentration and trajectory of blood proinflammatory factors increased in the PF after cardiac surgery over time [1]. Kramer et al. demonstrated an increase in the neutrophil infiltration in PF after 4 and 48 h postcardiac surgery over PF levels at time 0. Lipid peroxidation products of arachidonic acid–derived isoprostane 8-iso-prostaglandin F2α, and its stereoisomer 8-iso-15-prostaglandin F2α (F2 isoprostanes) were elevated in PF after 4 and 12 h following surgery and returned to PCF levels at time 0 after 24 to 48 h. Such increase of the levels of these pathological stimulants coupled with underlying atrial myocardial pathology can amplify the direct myocardial insult of a cardiac operation and may potentially contribute to the risk for postoperative AF [2]. As an opposite mechanism, it is also suggested that the elimination of the FP by pericardial drainage would reduce the pro-inflammatory injury. However, there is clinical evidence that increases complications and POAF occurrence [3]. Therefore, current evidence of how the composition of PF influences POAF and its change during surgery is inconsistent and requires further study.

Post-operative atrial fibrillation pathophysiology

Postoperative AF (POAF) frequently occurs as a complication of cardiac surgery with extracorporeal circulation, associated with an increased hospital stay, medical costs and overall mortality [4]. This arrhythmia has a high incidence, between 27 and 40%, despite the optimization in anesthetic protocols, surgical techniques, medical treatment and the wide use of antiarrhythmics such as beta-blockers and amiodarone [5]. Therefore, due to the suboptimal efficacy of perioperative pharmacological treatment, the search for new markers and pharmacological targets becomes necessary. Although the exact pathophysiology of POAF remains unclear, it is multifactorial in its origin. Patient related factors known to contribute include atrial dilatation: age-related fibrosis, cardiac structural damage, hypertension, and other comorbid conditions [6,7]. The concept of

Abstract

Atrial fibrillation (AF) is the most commonly encountered arrhythmia after cardiac surgery with extracorporeal circulation. Although usually self-limiting and represents an important predictor of increased patient morbidity, mortality and health care costs. Numerous studies have attempted to determine the underlying mechanisms of postoperative atrial fibrillation (POAF) with varied success. POAF comprises a multifactorial pathophysiology, in which inflammation and oxidative stress (OS) play a critical role. Studies have shown that microRNAs (miRNA), may be involved in the pathophysiology of AF determine a link between inflammation and OS occurrence. Also, in chronic patients, miRNAs have been implicated in AF-induced ion channel remodeling and fibrosis. However, the role of miRNA in POAF is not well defined. We will be tested the hypotheses that the development of POAF is associated with pro-inflammatory and pro-oxidant miRNA profile in blood, atrial and PF samples. These changes are attenuated by the administration of antagomiRs or microRNA mimics in ex vivo model of atrial fibrillation. In animal ex vivo model of AF, the effect of candidate miRNAs on the duration of arrhythmia and markers of oxidative stress, inflammation and mitochondrial dysfunction in cardiac tissue are presented. The contribution of miRNAs will be determined by blocking these candidate miRNAs with specific antagonists to establish effects on ex vivo AF duration and left ventricular function. The ex vivo model of AF could allow to define some molecular targets that would modulate these miRNAs, and contributes to cardiac arrhythmogenesis.

Pro-oxidant and pro-inflammatory Micro-RNAS profile as a risk factor for postoperative atrial fibrillation

Rodrigo L Castillo1,2*, Daniela F Henríquez3, Aníbal E Méndez4, Jorge G Farías4 and Catalina Carrasco-Pozo5

1Departamento de Medicina Interna Oriente, Facultad de Medicina, Universidad de Chile, Santiago, Chile
2Unidad de Paciente Crítico, Hospital del Salvador, Santiago, Chile
3Departamento de Fisiopatología, Programa de Ayudantes Alumnos, Facultad de Medicina Oriente Universidad de Chile, Santiago, Chile
4Departamento de Ingeniería Química, Facultad de Ingeniería y Ciencias, Universidad de La Frontera, Francisco Salazar, Chile
5Discovery Biology, Griffith Institute for Drug Discovery, Griffith University, Nathan, QLD 4111, Australia

*Correspondence to: Rodrigo L Castillo, Departamento Medicina Interna Oriente, Facultad de Medicina, Universidad de Chile, Unidad de Paciente Crítico, Hospital Salvador, Santiago, Chile, E-mail: rcastillo@med.uchile.cl; rodrigouch@gmail.com

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local oxidative stress. The release of mediators such as cytokines, chemokines and adhesion molecules, all of which exacerbate the tissue damage, even areas of necrosis of the myocardial fiber can be generated [30,31]. The next step, the repair involves the risk of collagen deposition in the extracellular matrix, a process of interstitial fibrosis that would affect the functional properties, both electrical and mechanical, of the myocardium. Thus, in vitro studies, increase ROS concentration have shown affect the contractile function of cardiomyocytes associated with calcium overload and major sensitivity of myofilaiments, as a arrhythmogenic mechanism [32,33].

Mitochondrial function

Recent experimental evidence suggests that changes of levels of phosphocreatine, electron transfer chain proteins and differences in mitochondrial distribution play a role in AF [34]. Mitochondrial dysfunction leading to mitochondrial ROS production is implicated in ryanodine receptor oxidation facilitating Ca\(^{2+}\) leak and AF development [35,36]. Also, an interesting ex vivo study using atrial tissue from patients with and without AF showed that inward calcium L-type channels remodeling contributes to mitochondrial oxidative stress and increased expression of oxidative markers and adhesion molecules while antioxidants and inhibition of NF-κB attenuate these changes [37,38]. Myeloperoxidase (MPO), an enzyme released from activated polymorphonuclear neutrophils has been linked to atrial fibrosis and remodeling [39]. MPO catalyzes the generation of reactive species like hypochlorous acid which affect intracellular signaling cascades in various cells and advance activation of pro-metaloproteinases and deposition of atrial collagen resulting in atrial arrhythmias. In an experimental setting MPO-deficient mice or rabbits were protected from AF [40,41]. In the same study, humans with AF had higher plasma concentrations of MPO and a larger MPO burden in right atrial tissue compared to control subjects. Furthermore, a recent study examining right atrial tissues from patients undergoing cardiac surgery indicated that monoamine oxidase represents an important source of ROS in human myocardium associated with POAF along with glutathione peroxidase [42]. However, it is currently unknown whether the mechanisms of mitochondrial dysfunction and eventual calcium overload would have a relevant pathogenic role in the development of POAF.

Inflammation and POAF

There is consistent evidence to support the influence of a surgery-related acute inflammation on the pathogenesis of POAF. This is largely based on association between levels and activity of white blood cells and incidence of POAF. Patients who have higher postoperative leukocytes count are significantly more likely to develop POAF [43-46] and patients undergoing POAF tend to have greater degree of monocyte activation as seen by higher expression of CD11b [47,48]. Moreover, the elevated pre and postoperative neutrophils/lymphocytes ratio in patients undergoing coronary bypass graft surgery can be associated with an increased incidence of POAF [49,50]. Exactly how these blood components can trigger POAF is not known. Previous work using animal models has shown that when activated neutrophils bind to cardiac myocytes they can cause changes in myocyte electrical activity that could be arrhythmogenic [51,52]. Cardiac surgery can induce a systemic inflammatory state (systemic inflammatory response syndrome, SIRS), whose cellular mechanisms of generation include the participation of ROS [45,53]. This systemic response is associated with the activation of cytoplasmic transcription factors such as NF-kB, which is key in the regulation of the inflammatory, immune, proliferative and apoptotic
response [45,54]. In the case of NF-κB, the ROS, especially H₂O₂, would act at least at two levels: 1) oxidation of key kinases in the activation of IkB Kinase which activates the NF-κB [55,56] and, 2) Modulation of the transport of this factor from the cytoplasm to the nucleus [45,57,58]. Systemic inflammatory response syndrome has a mild modality, but on the occasion of prolonged surgeries or exaggerated elevation of serum cytokines, especially IL-6, it can progress to a severe systemic inflammatory state, with lethal consequences [3,59] and it is likely that oxidative stress determines this difference. Markers of oxidative stress and inflammation are usually very ubiquitous in cardiac IR injury, therefore other markers that increase the specificity of the diagnosis in this type of arrhythmias are clinically needed. The contribution of oxidative stress and inflammation are shown in Figure 1.

mi-RNA and cardiovascular pathology

MicroRNAs (miRNA) are a class of small non-coding RNA (20-25 nucleotides) that participate in gene regulation. In recent years, miRNAs have emerged as a key epigenetic mechanism in the development and functionality of the cardiovascular system. These molecular species regulate basic functions in virtually all cell types and therefore are directly associated with the pathophysiology of a large number of cardiovascular diseases [60,61]. Since its relatively recent discovery in extracellular fluids, miRNAs have been studied as potential biomarkers of several diseases. There are numerous studies that propose miRNAs as circulating biomarkers of different cardiovascular pathologies (myocardial infarction, coronary heart disease or heart failure, among others), even with physicochemical and biochemical properties superior to the conventional protein indicators currently used in clinical practice. They can be isolated from a variety of samples such as cell-conditioned media, plasma, serum, and other bodily fluids using a range of different methods such as sequential ultracentrifugation, density gradient separation, ultrafiltration, and commercial kits [62]. Currently, cardiovascular risk assessment is based exclusively on an intramuscular or systemic application of these agents currently based on an intramuscular or systemic application of these traditional risk factors [63]. Unfortunately, these traditional risk factors do not experience any cardiovascular episode; not even in the long term. Thus, there is a clear clinical interest in the development of new non-invasive and easily accessible biomarkers that significantly improve the predictive capacity of the algorithms developed to date, beyond the traditional risk factors [63].

mi-RNA and atrial fibrillation

The role of miRNA in cardiac arrhythmogenesis is in growing study in clinical and basic models [64]. miRNA targeting pathways associated with the regulation of cardiomyocyte metabolism (miR-208a and miR-223) may alter the provision of energy substrate required to maintain AF [65], whereas other miRNAs are thought to play a central role in changes associated with structural (miR-133, miR-590, miR-29b, miR-208, miR-638 and miR-150) and electrical remodeling of the cardiac tissue (miR-328, miR-1 and miR-153), and therefore other markers that increase the specificity of the diagnosis in this type of arrhythmias are clinically needed. The contribution of oxidative stress and inflammation are shown in Figure 1.
other markers such as the classical oxidative stress and inflammation, generating a new type of diagnostic cluster in POAF.

Conclusion

Despite the evidence of oxidative stress, inflammation and apoptosis occurrence in the atrial tissue and plasma of POAF patients post cardiac surgery with extracorporeal circulation, miRNA expression profiling results revealed a clear dissociation in expression levels between the atrial appendage and blood circulation. Whereas, an increase in some miRNA candidates such as higher levels of miR-1 and a decreased in miR-133A that specifically negatively correlated with apoptosis was observed in the atrial tissue; however, the miR plasma equivalents were similar to their pre-CABG levels correlated with apoptosis was observed in the atrial tissue; however, an improved understanding of miR function would facilitate the design of novel strategies for cardio-protection against atrial tissue remodeling in POAF patients.

Finally, the use and validation of new markers such as miRNA in cardiac tissue and different fluids is important since their different expression profiles could bring us in a non-invasive way to what is induced by ischemia-reperfusion in myocardial tissue, its relationship with atrial remodeling and probable pharmacological targets that can be modelled.

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