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DIANA

KAIREVIČIŪTĖ

THE SIGNIFICANCE OF DIFFERENT BIOMARKERS IN THE PREDICTION OF THE DEVELOPMENT OF ATRIAL FIBRILLATION AFTER CARDIAC SURGERY

Doctoral dissertation

Biomedical science, Medicine (06B)

Vilnius, 2014

The study was carried out at Vilnius University during 2009 – 2013

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ĮVAIRIŲ BIOMARKERIŲ REIKŠMĖ PRIEŠIRDŽIŲ VIRPĖJIMO KILIMUI PO ŠIRDIES OPERACIJŲ

Daktaro disertacija

Biomedicinos mokslai, medicina (06B)

Vilnius, 2014 metai

Disertacija rengta 2009 – 2013 metais Vilniaus universitete

Mokslinis vadovas:

Prof. dr. Audrius Aidietis (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B).

ACKNOWLEDGEMENT

I thank professor Gregory Lip for scientific supervision and help with the all laboratory work. The contribution of the Haemostasis, Thrombosis and Vascular Biology Unit, University of Birmingham, UK is acknowledged.

I was funded by a research fellowship awarded by the European Society of Cardiology.

ABBREVIATIONS

ACE – angiotensin converting enzyme
ACEI – angiotensin converting enzyme inhibitor
ACT – activated clotting time
ADAM – a disintegrin and metalloproteinase
AF – atrial fibrillation
ARB – angiotensin receptor blocker
CABG – coronary artery bypass grafting
CHF – congestive heart failure
CI – confidence interval
CPB – cardiopulmonary bypass
Cx – connexin
ECG – electrocardiogram
EDTA – ethylene-diamine-tetraacetic acid
ELISA – enzyme-linked immunosorbent assay
ERP – effective refractory period
EF – ejection fraction
Eg. – exempli gratia
Etc. – et cetera
Hs-CRP – high sensitivity C-reactive protein
IAA – isolated atrial amyloidosis
ICU – Intensive Care Unit
IL – interleukin
ICa – L-type Ca+2 current
IKs – slow delayed rectifier K+ currents
IKur – ultra-rapid delayed rectifier K+ current
INCX – Na+/Ca+ exchange channels
Ito – transient outward current

IQR – interquartile range

LA – left atrium

LAA – left atrial appendage

LAPW – left atrial posterior wall

LV – left ventricular

MMP – matrix metalloproteinase

mRNA – mitochondrial ribonucleic acid

MVS – mitral valve surgery

NADPH – nicotinamide adenine dinucleotide phosphate

NO – nitric oxide

OR – odds ratio

PAI – plasminogen activator inhibitor

PB – peripheral blood

PBS – phosphate-buffered saline

PUFAs – n-3 polyunsaturated fatty acids

RA – right atrium

RAA – right atrial appendage

RAAS – renin-angiotensin-aldosterone system

RCT – randomized controlled trial

SD – standard deviation

SR – sinus rhythm

TF – tissue factor

TGF-beta – transforming growth factor beta

TIMP – tissue inhibitor of matrix metalloproteinase

TNF-alpha – tumor necrosis factor alpha

VCAM – vascular cell adhesion molecule

vWF – von Willebrand factor

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1. INTRODUCTION

Atrial fibrillation (AF) is a common complication of cardiac surgery, with an increasing incidence. Postoperative AF results in many complications and increased healthcare resources. The increase in post-operative AF may be due to reduction of contraindications for cardiac surgery, population ageing, and better arrhythmia diagnostic methods. The reported prevalence and incidence of AF after cardiac surgery varies among different studies, depending on population profile, type of surgery, arrhythmia definition and detection methods, design of study. A higher incidence of postoperative AF has been reported after valvular surgery (33% – 49%) [1] and combined valvular/coronary artery bypass grafting (CABG) surgery (36% – 63%) [1 – 2], whereas the lowest – after heart transplantation (11%) [2]. The incidence of postoperative AF is much higher compared to the general population, even amongst older patients, and compared to non-cardiac surgery patients [1].

The frequency of AF occurrence after CABG has been reported from 5% to 70% [3 – 4], although this wide range is dependant upon the population profile, arrhythmia definition, detection methods, and study design. A recent meta-analysis of 24 randomized controlled trials found the incidence of AF after CABG of around 26% (95% CI 24.7-29.1) [5]. One large, prospective, observational, international, multicenter study of 4657 patients reported postoperative AF in 32.2% of patients undergoing isolated CABG surgery [6]. Interestingly, this seems to vary between different geographical regions: for example, in the USA – 33.7 %, Canada – 36.6 %, Europe – 34.0 %, the UK – 31.6 %, Middle East Europe – 41.6 %, South America – 17.4 %, and Asia – 15.7 % [6]. The prevalence also varied by monitoring methods, with most arrhythmia episodes (76.8%) diagnosed using continuous electrocardiogram (ECG) monitoring, compared to 17.5% by 12-lead ECG and only 12.8% by physical examination [6]. Almost all AF episodes occur within the first 6 days following cardiac surgery with

the highest incidence rate on the second or third postoperative day [6 – 7], that coincides with a peak of systemic inflammation caused by surgery [8] as well as elevated atrial stretch due to increased intravascular volume [9].

This common and, at first sight, "benign" arrhythmia after cardiac surgery is associated with many complications and some of them are life threatening. AF after CABG is associated with an increased early and late mortality rate after cardiac surgery [6, 10 – 13], stroke [10, 12, 14 – 15], prolongation of hospital stay [10 – 12, 15 – 16] (Table 1). Overall, the risk for death is increased by 9.7% (range 3% – 33.3%). Other complications include persistent congestive heart failure symptoms, respiratory failure, various infections, renal failure, hypotension and shock, multisystemic failure and cardiopulmonary arrest [10, 12]. In addition, postoperative AF is associated with prolonged hospital stay [16], increased hospital and health care costs, patients undergo more investigations [10]. For example, Mathew et al [6] identified that more axial computer tomography and ultrasonography tests were performed in patients after AF onset following cardiac surgery, and 35% of patients with postoperative AF were discharged to an extended care facility, compared with 28% who remained in sinus rhythm (SR).

Many clinical variables associated with the development of postoperative AF have been assessed. However, there is controversy over the significance of most clinical features, and only advanced age has the strongest evidence [10, 12, 17]. Despite the diversity of presentations, the precise mechanisms of AF related to cardiac surgery are not well understood. A wide variety of reasons has been proposed for the pathogenesis of this common arrhythmia. A better understanding of pathophysiological aspects of postoperative AF may allow insights into preventive strategies and broaden treatment options.

Inflammation has been implicated in the pathogenesis of post-CABG AF [18 – 20]. For example, abnormal levels of high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) are biomarkers of inflammation, which have been shown to be

raised in patients with non-valvular AF, independently of other risk factors [19, 21 – 22]. Structural alterations in atria in AF may be a consequence or predictor of this condition [23 – 24]. Biomarkers of extracellular matrix remodelling and turnover, such as matrix metalloproteinase-9 (MMP-9), and its inhibitor, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) have been shown to reflect atrial structural changes that may maintain AF [25 – 26]. However, the place of these and related markers is unclear, especially in predicting which patients are likely to go on to develop AF after CABG. An alternative pathophysiology to inflammation in cardiovascular disease is atherothrombosis, and the two may be linked as an inflammatory environment within the heart. An inflammation may 'drive' the prothrombotic state in AF, which may contribute to the increased risk of thrombogenesis and subsequently, potentially fatal thromboembolism [27 – 28]. Indeed, perhaps the major consequence of AF is thrombotic stroke, leading to the hypothesis that AF itself is a prothrombotic disease [29]. Evidence in favour of this hypothesis includes increased levels of plasma markers of a prothrombotic state (von Willebrand factor (vWF), fibrinogen, and fibrin D-dimer) in the plasma of patients with AF [27, 30]. However, a weakness of this approach is that blood taken from a peripheral vein may not necessarily reflect the situation within the heart, although there is evidence that levels of certain cytokines in peripheral blood do mirror intracardiac levels [31].

Nevertheless, the extent to which inflammatory and extracellular matrix remodeling processes influence the development of AF after CABG has not been adequately tested. In particular, it is not clear whether concentrations of plasma biomarkers obtained from peripheral blood are similar to levels of the same markers within chambers of the heart. Moreover, the extent to which the expression of inflammatory, remodeling and prothrombotic molecules by the tissue of the heart is important in the development of AF is unknown.

The first hypothesis tested in the present study was that biomarkers indicative of the following pathophysiological processes, that are: 1) inflammation (hs-CRP and IL-6), 2) extracellular matrix remodelling (MMP-9 and TIMP-1),

and 3) the prothrombotic state (tissue factor (TF) and vWF), were predictive of postoperative AF amongst patients undergoing CABG, and that differences in the variation of these biomarkers in the peripheral circulation would directly reflect those specific to intracardiac chambers. The second hypothesis was that the intracardiac tissue expression of the defined markers is indicative of the same pathophysiological processes that are predictive of postoperative AF after CABG surgery.

Table 1. Postoperative atrial fibrillation and outcomes

Authors, year	**N of patients, type of surgery**	**In-hospital mortality: post. AF vs. no post. AF**	**Late mortality: post. AF vs. no post. AF**	**Length of stay (days): post. AF vs. no post. AF**	**Stroke: post. AF vs. no post. AF**
Aranki et al, 1996 [10]	570, CABG	3.9% vs. 1.8%, p=0.15	NS	15.3 ± 28.6 vs. 9.3 ± 19.6, p=0.001;	3.7% vs. 1%, p=0.025
Almassi et al, 1997 [1]	3794, CABG, valvular, combined	5.95% vs. 2.95%, p=0.001 (30 days)	9.36% vs. 4.17%, p=0.001 (6-month)	Median: ICU: 3.6 vs. 2, p<0.001; Hospital: 10 vs. 7, p<0.001; Readmission to the ICU: 13.49% vs. 3.52%, p<0.001	5.3% vs. 2.4%, p<0.001
Borzak et al, 1998 [18]	436, CABG	NS	NS	(adjusted multivariate analysis) 9.2 ± 5.3 vs. 6.4 ± 5.3, p<0.001	NS
Tamis and Steinberg, 2000 [16]	216, Elective CABG	NS	NS	15.1 ± 9.0 vs. 10.0 ± 4.6, p<0.001; Adjusted multivariate analysis: AF patients stayed 3.2 +/- 1.7 days longer, p<0.001	NS
Stamou et al, 2000 [11]	969, off-pump CABG	3% vs. 1%, p=0.009 (in-hospital)	NS	9 ± 6 vs. 6 ± 5, p<0.001	NS
Stamou et al, 2001 [14]	16 528, CABG	NS	NS	NS	Post. AF as a predictor for stroke: OR 1.7, 95% CI 1.4-2.2, p<0.001

Authors, year	N of patients, type of surgery	In-hospital mortality: post. AF vs. no post. AF	Late mortality: post. AF vs. no post. AF	Length of stay (days): post. AF vs. no post. AF	Stroke: post. AF vs. no post. AF
Likosky et al, 2003 [15]	11 825, CABG	NS	NS	NS	2.7% vs. 1.2%, p<0.001; Post. AF as a predictor for stroke: OR 1.82, p<0.001
Villareal et al, 2004 [12]	6 475, CABG	7.4% vs. 3.4%, p=0.0007 (in-hospital)	Post. AF as independent predictor: adjusted OR 1.5, p<0.001 in retrospective cohort, and OR 3.4, p=0.0018 in case-matched group (mean follow-up 5 years)	Median: 14 vs. 10, p<0.0001	5.2% vs. 1.7%, p<0.0001;
Mathew et al, 2004 [6]	4 657, CABG	4.7% vs. 2.11%, p<0.001	NS	Median (IQR): ICU, hours: 36.3 (21.7-68.2) vs. 25.5 (21.0-47.3), p<0.001; Hospital, days: 9 (7-12) vs. 7 (6-10), p<0.001	No significant association
Auer et al, 2005 [7]	253, CABG, valvular, combined	NS	NS	(adjusted multivariate analysis): 14.2 ± 5.3 vs. 10.8 ± 3.8, p<0.01	NS
Ahmadi et al, 2007 [13]	11 183, CABG	33.3% vs. 1.07%, p<0.05 (24 hours)	NS	NS	NS
Ahlsson et al, 2010 [17]	571, CABG	NS	29.7% vs. 14.8% (p<0.001). Median follow-up 6 years	NS	NS

CABG – coronary artery bypass grafting, CI – confidence interval, ICU – intensive care unit, IQR – interquartile range, NS – not stated; OR – odds ratio, post. AF – postoperative atrial fibrillation. P < 0.05 considered as significant.

1.1. The aim of the study:

To investigate the prognostic value of plasma and atrial tissue expression of prothrombotic, proinflammatory and extracellular matrix turnover indices for the development of AF after CABG surgery and to describe atrial ultrastructural changes in patients suffering from severe coronary artery disease.

1.2. Objectives:

1. To determine peripheral and intracardiac plasma levels of cytokines (hs-CRP, IL-6, vWF, TF, MMP-9 and TIMP-1) and relate them to the development of AF after CABG surgery.
2. To compare plasma cytokines (hs-CRP, IL-6, vWF, TF, MMP-9 and TIMP-1) levels between peripheral blood and different intracardiac chambers (right atrium, right atrial appendage, left atrium, and left atrial appendage).
3. To examine tissue expression of biomarkers (IL-6, vWF, TF, MMP-9 and TIMP-1) in both atrial appendages in patients undergoing CABG surgery and relate it to the development of postoperative AF.
4. To compare tissue expression of biomarkers (IL-6, vWF, TF, MMP-9 and TIMP-1) by the left atrial appendage (LAA) and right atrial appendage (RAA) tissue in patients undergoing CABG surgery.
5. To examine and describe atrial ultrastructural changes using transmission electron micrsoscopy in patients undergoing CABG surgery.

2. LITERATURE REVIEW

2.1. Search strategy

The thorough search of published medical literature was performed using electronic bibliographic databases such as MEDLINE, EMBASE, COCHRANE DATABASE, which was not restricted only to the English language. We applied the following terms for the search: “atrial fibrillation”, “cardiac surgery”, “atrial remodeling”, “inflammation”, “cytokines”, “thrombogenesis”, “prevalence”, “prevention” etc.. Additionally, we reviewed the references of identified articles. A hand search for abstracts from international meetings and supplements of some major journals was also performed.

2.2. Pathophysiological mechanisms of atrial fibrillation and atrial remodeling

The pathophysiological mechanisms of postoperative AF have been described in a large amount of clinical and experimental trials but still are for the moment far from being fully elucidated. The extensive studies on postoperative AF show us that it is multifactorial. Some mechanisms of postoperative AF are identical to non-surgical AF, and an occurrence of postoperative AF is strongly determined by the pre-existence of an AF substrate. Maesen et al classified risk factors of postoperative AF to acute (related to the surgery, such as inflammation, adrenergic stimulation) and chronic that can be determined by structural heart disease or age [33].

2.2.1. Electrophysiological considerations

Theoretically, postoperative AF should be initiated and maintained by the same classical electrophysiological mechanisms – ectopy, single rotor with fibrillatory conduction and multiple circuit reentry – that were first described in the beginning of the last century and still form the basis of our understanding of AF

pathophysiology [34]. Later, the multiple wavelet theory of AF was proposed, whereby this arrhythmia can be sustained by multiple propagating waves in the presence of short and heterogeneous refractoriness of atrial myocardium [35]. Alessie et al [36] demonstrated this theory in an experimental model.

Thus, AF can be sustained by reentry, which is triggered generally by a premature beat (ectopic activity). If premature beats are rapid and sustained, they may maintain AF by themselves. In other cases, the premature beat may initiate reentry that perpetuates in an atrial tissue under appropriate circumstances. Indeed, an electric impulse that forms a reentry circuit and promotes AF, terminates spontaneously due to normal conduction and refractoriness of surrounding atrial tissue. In cases of shortening of the refractory period and/or prolonging conduction velocity in the atrial myocardium, a path of the propagating electric impulse that forms reentry circuit decreases and causes a larger number of functional reentry circuits (the so-called "rotors") which are accommodated within a given mass of (atrial) tissue with a sufficient number of unexcited myocytes [37]. Typical triggers able to evoke ectopic atrial activity are the presence of abnormal activity of the autonomic nervous system [38], atrial stretch or rapidly firing ectopic foci located within the pulmonary veins [39].

Particular conditions related to the surrounding atrial tissue are requirements for the arrhythmia initiation and maintenance. The functional and structural changes in the atrial myocardium that promote atrial tachyarrhythmias are referred to as 'atrial remodeling', with evidence of functional and structural alterations in the atrial myocardium. Two main forms of atrial remodeling have been described in animal models of AF: electrical or functional remodeling, and structural (anatomical, architectural) atrial remodeling. Atrial fibrillation also changes electrical atrial properties by itself and can stabilize AF or facilitate reinduction of arrhythmia – "AF begets AF" [40]. Indeed, rapid atrial rates reduce duration of an action potential leading to the shortening of effective refractory period (ERP) in the atrial myocardium.

Recently, Allessie et al demonstrated that epicardial breakthrough of waves propagating in deeper layers of the atrial wall and electric dissociation of neighboring atrial muscle bundles are key elements in the development of the substrate of persistent AF [41 – 43].

2.2.2. Structural changes

Atrial enlargement as a risk factor for AF occurrence has been long-established [44]. As previously, the first animal studies suggestive of structural (apart from electrical) atrial remodeling were models of congestive heart failure (CHF) and AF, where induced CHF caused initiation of AF without any shortening in ERP [37]. Li et al also showed that the duration of provoked AF in CHF dogs is comparable with AF seen in the tachycardia-induced electrical atrial remodeling setting. This can be related to the heterogeneity of conduction velocity within atrial myocardium caused by local areas with delayed conduction, and the histological evaluation of atrial tissue revealed pronounced interstitial fibrosis when compared with controls ($p < 0.01$) or atria with tachycardia-induced remodeling ($p < 0.01$) [37]. Analogous fibrotic changes in atrial myocardium were described much earlier, in overloaded [volume or/and pressure] atria in animal models [45] as well as clinical studies [46 – 47]. Li et al [37] were the first to relate electrical atrial remodeling to a structural one.

Ultrastructural changes in fibrillating animal atria, which showed such signs of myolysis [eg., loss of myofibrils], accumulation of glycogen, altered shape and size of mitochondria, fragmented sarcoplasmic reticulum and scattered nuclear chromatin have been described, although the degree of such marked cellular abnormalities were not significantly associated with duration of AF [48]. Similar ultrastructural abnormalities have been seen in electrically remodeled (defined by shortened ERP) animal atria caused by long-lasting (6 weeks) rapid atrial pacing, and these changes were most pronounced in the left atrial (LA) posterior wall [49].

2.2.3. Ion channels and electrical remodeling

In a classic animal experimental model, Wijffels et al induced AF in goats and showed that the inducibility of further AF episodes was facilitated and duration of AF paroxysms was prolonged together with the abbreviation of atrial ERP [40]. In the animal study by Yue et al the abbreviation of ERP in response to very rapid atrial pacing rate was evaluated and related to cellular and ionic changes [50]. They established that shortening of ERP is preceded by decreasing action potential duration, which declines due to a reduction of the transient K+ outward current (Ito) and L-type Ca+2 current (ICa) [50]. Ionic atrial remodeling is different in a canine CHF model, whereby the action potential was not changed or slightly increased, Ito and ICa, as well as IKs (the slow delayed rectifier K+ currents) were reduced, and densities of T-type Ca+2 current channels and Na+/Ca+ exchange (INCX) channels were more intense [51]. Reduced ultra-rapid delayed rectifier K+ current (IKur) was found in human persistent AF [52]. Only a non-significant trend towards a decrease in IKur was found in patients with postoperative AF [52]. In addition, Swartz et al did not detect any differences in atrial K+ channels between patients with and without postoperative AF [53].

The Na+/Ca+ exchanger carries transient inward currents that promote delayed afterdepolarization, and hence, triggered activity [54]. Indeed, delayed afterdepolarization potentials might contribute to the development of atrial tachyarrhythmia in CHF dogs, if an appropriate structural substrate is present. Mitochondria with disintegrated structure of cristae have been suggested as such a substrate [55] where increased transient inward currents caused by CHF as well as structural atrial remodeling, triggers AF. Triggered activity can also be promoted by hypercatecholaminaemia, tissue stretch and various metabolic changes that exist in CHF.

Studies on ionic remodeling in human atria have been performed [56-58] although interpretation of ionic channels alterations in human atrial remodeling

is complicated by many different pathological settings, comorbidities and miscellaneous medications taken by AF patients.

Van Wagoner et al found a larger density of ICa in isolated myocytes in patients developing postoperative AF compared to those without AF [59]. In addition, a higher adrenergic activation after cardiac surgery [60] can increase calcium influx through L-type calcium channels and it can contribute to triggered activity (for example, delayed afterdepolarizations) potentially initiating AF after cardiac surgery [59]. Nevertheless, Workman et al did not found any differences in ICa density between patients developing postoperative AF and remaining in SR after the cardiac surgery [61].

Electrical atrial remodeling is reversible and short-lasting condition, but – in contrast – the inducibility of AF continues much longer, suggesting structural atrial remodeling causes, rather than an electrical one. Indeed, shortened ERP caused by long-lasting AF recovers within 7 – 14 days after the cardioversion from AF, whereas the duration of impulse propagation increases after restoration of SR and is prolonged for much longer [62]. Longer restoration of atrial conduction velocity compared with altered ERP has been shown also in atrial electrical remodeling induced by long-lasting rapid atrial pacing in dogs [63].

Conduction disturbances presented in fibrillating atria have been reported [64], whereby inducibility and spontaneous initiation of AF are facilitated after recovery of a shortened atrial ERP following restoration of SR. They have been related to atrial dilatation and ultrastructural abnormalities (eg. changes in myocytes diameter, ruptured sarcomers, increased spaces between myofibrils, increased size and number of mitochondria, active nuclei), which last much longer than electrical atrial changes, and were found more pronounced in the right atrium (RA).

The hypothesis of a link between conduction disturbances and structural atrial changes was proven by Neuberger et al, who compared the electrophysiological properties of AF in dilated and normal atria, where there was an association

between conduction delay and size of myocytes [65]. Conduction velocity delays in atria may also be caused by decreased density of Na+channels, at least in an animal model of chronic AF [66].

Recently, total atrial conduction time measured preoperatively in the LA by tissue-Doppler imaging was found significantly longer in patients who developed AF after cardiac surgery compered with those remained in SR ($p < 0.001$) and it correlated with the degree of atrial fibrosis ($r = 0.73$, $p < 0.01$) [67].

2.2.4. Connexins

Mice absent of the gap-junctional protein connexin (Cx) Cx40 in their atrial myocardium were more susceptible to supraventricular arrhythmias [68]. Later, the relation of Cx40 to atrial conduction properties was determined [69]. Nevertheless, the amount of Cx40 is restored following the recovery of SR after 2 months, although the susceptibility to the persistence of AF remains even after 4 months [70]. The same study described ultrastructural abnormalities in the fibrillating atria including myolysis, increased myocyte diameter, accumulation of glycogen, mitochondrial changes and an abundance of extracellular matrix [70].

Data of human studies on Cxs are also available. A decrease of Cx40 in human fibrillating atria was reported by Kostin et al [71] with a relationship to increased collagen type I in the fibrillating RA. In contrast, Nao et al did not find any association between diminished Cx40 expression in the RA from patients with chronic AF secondary to mitral valve disease, nor to the degree of fibrotic tissue [72]. Wilhelm et al investigated the distribution of Cx40 and Cx43 in human RAA and related their findings to underlying rhythm and fibrosis [73]. They found a decrease of Cx40 and the difference in the ratio of Cx40 to Cx43 in RAA obtained from patients with persistent AF; however, there was no correlation with degree of fibrotic changes [73], suggesting that gap-junctional remodeling occurs earlier than structural.

Severino et al [74] showed a downregulation of Cx43 protein expression by hypoxia and ischemia, and contributed it to a possible mechanism of AF onset and/or maintenance after cardiac surgery. Despite many studies supporting the impact of a downregulation of atrial Cxs on the pathogenesis of AF, Li et al reported that atrial inflammation and fibrosis status before CABG, but not the changes of Cxs, are associated with postoperative AF [75].

2.2.5. Autonomic nervous system

An abnormal activity of autonomic nervous system can provoke ectopic atrial foci [38]. The postoperative period is associated with increased sympathetic activity as shown by enhanced heart rate variability just before the initiation of AF following CABG surgery [76 – 77]. Impaired baroreflex sensitivity preoperatively has been found associated with the development of AF within 1 week after cardiac surgery [78]. There is still negotiable question if the sympathetic activation is related to increased activity or loss of vagal tone [76 – 77]. Of note, the peak of sympathetic activation occurs within 24 hours after the cardiac surgery, and the peak of postoperative AF is on the second or third day after the surgery.

Interestingly, the most important risk factor of postoperative AF is advanced age, and it is associated with increased circulating norepinephrine levels [79].

Ventral cardiac denervation was even suggested for the prevention of postoperative AF [80]. However, the later studies did not reveal any benefit of ventral denervation in prevention of postoperative AF [81 – 82]. Moreover, Omran et al demonstrated the ventral cardiac denervation as a predictive factor for the development of AF after CABG [83].

Additionally, administration of inotropic agents during and after the cardiac surgery is associated with postoperative AF [84 – 85]. Although postoperative administration of beta-blockers did not reduce the incidence of AF after the cardiac surgery markedly [61, 86], the discontinuation of beta-blocker therapy

before the surgery increased the occurrence of AF more than two-fold [87]. Of course, it should be explained not only by higher activity of adrenergic system after the cardiac surgery, but also by the rebound phenomenon of beta-blockers withdrawal.

2.2.6. Fibrosis and structural remodeling

Fibrosis is recognized as a hallmark of atrial structural remodeling, and it is only partially reversible process, finally leading to sustained AF [75]. Atrial fibrosis occurs in many pathophysiological settings, including ageing, heart failure, valve disease, coronary artery disease [88 – 95].

Shingava et al [88] showed that not only atrial fibrosis is responsible for propensity for AF in CHF, but also the haemodynamic, architectural cardiac changes, neurohumoral mechanisms, tissue stretch that are presenting in this particular condition. Recently, Burstein et al reported that atrial myocytes affected by a rapid rate produce substances, which activate myofibroblasts, providing a plausible pathophysiological mechanism where atrial fibrotic process is evoked by AF [89]. Thus, atrial structural and ultrastructural changes have a critical impact in susceptibility for AF as well, as in maintenance of arrhythmia.

Thus, atrial structural remodeling involves the loss of myocytes (due to apoptosis or necrosis), cellular hypertrophy, sarcomerolysis, mitochondrial dysfunction, contractile dysfunction, endocardial damage/dysfunction, myocyte dedifferentiation, fibrosis and amyloid deposition [90]. Structural atrial remodeling is a result of intracellular calcium overload caused by frequent depolarization of membrane and calcium influx through L-type calcium channels, and of underlying structural heart disease. Increased cytosolic calcium handling also induces many physiologic cell-protective mechanisms through different signal transduction pathways. Cardiac fibrosis, as defined by marked changes in the extracellular matrix with interstitial accumulation of collagen, usually accompanies myolysis [91].

Intracellular calcium also activates the calcium-dependent proteases, calpains – which in turn results in the degradation of contractile proteins and mechanical atrial dysfunction that persists after restoration of SR [92].

Alongside the increased production of collagen during atrial structural remodeling process, an altered turnover of extracellular matrix has been shown by differences in MMPs and their inhibitors – TIMPs expression, activity and proportions [93]. These may be responsible to dilation of atria during AF [94].

Atrial fibrosis can occur as a result of the mechanical overload of the atrial tissue in combination with the action of many profibrotic factors [95].

The fibrotic process in the tissue is regulated by many hormones and cytokines, including transforming growth factor-beta (TGF-beta) family members, the renin-angiotensin-aldosterone system (RAAS), fibroblast growth factors and tumor necrosis factor-alpha (TNF-alpha) [96]. Without the accumulation of collagen in atrial remodeled myocardium, other degenerative processes such as atrial amyloidosis has been implicated [97].

TNF-alpha has been shown to be a potential proapoptotic stimulus [98]. The role of TGF-beta1 in the pathogenesis of atrial fibrosis has also been demonstrated with transgenic mice that overexpress this cytokine in their hearts. Indeed, TGF-beta1 is implicated into conversion of fibroblasts to myofibroblasts and hence, regulates the turnover of collagen [99], although TGF-beta1 is not implicated in cellular electrophysiology, and fibrosis by itself can be sufficient substrate for the promotion of AF, at least in animal models [100].

Transgenic mice with angiotensin converting enzyme (ACE) overexpression result in the development of atrial fibrosis [101]. Cytosolic calcium also activates calmodulins and calcineurin, and hypertrophy is induced [102], and increased levels of cardiac troponin I, atrial natriuretic peptide and beta-myosin heavy chain reflect this process [103].

Therefore, large evidence suggests that atrial structural remodeling is a result of complex interactions among neurohormonal and cellular mediators.

There is evidence from experimental studies that atrial fibrosis is associated with decreased velocity and increased heterogeneity of electrical conduction [70, 100, 104]. Collagen fibers compose electrical barriers and cause asynchronous propagation of electrical impulse [105]. The electrical barriers make adjacent regions of diverging refractory periods and can promote reentry [106]. In addition, direct interactions between fibroblasts and myocytes contribute to electrophysiological alterations in atrial tissue [107].

2.2.7. Histopathology of human fibrillating atria

Atrial histopathological abnormalities relating to atrial fibrillation are summarized in Table 2. However, it is still uncertain whether the structural and ultrastructural atrial changes contributed to AF development or whether it was AF by itself that caused myocardial alterations.

One of the first studies investigating human atrial structural abnormalities and the relation to AF was published by Frustaci et al [108]. They assessed atrial biopsies taken from the interatrial septum in 12 patients who suffered from lone AF using light and transmission electron microscopy. No histological abnormalities were revealed in the samples taken from the control group, but histological changes corresponding to histopathological Dallas criteria of myocarditis were found in most atrial biopsies from the AF subjects (Table 2) [108].

In a case-control study, atrial expression of fibrosis and extracellular matrix proteins was determined in lone AF, AF related to mitral valve disease, and those in normal SR in LA biopsies obtained from 118 patients [109]. Marked fibrotic changes were revealed in the left atrium in the presence of AF, compared to sparse connective tissue in the left atrium of SR group patients, where coupling of myocytes was not disrupted by fibrotic fibrils. There was markedly higher (almost 3-fold) expression of collagen (particularly, of collagen type I) in fibrillating LA. Also, the expression of collagen type III was different in the LA obtained from patients with lone AF compared to that with AF related to mitral

valve disease, although expression of major extracellular matrix proteins did not differ between both AF groups, and fibronectin was not found associated with any type of AF [109]. Thus, left atrial structural remodeling related to AF is due to expression of collagen type I. The further overloading of the LA by pressure and volume leads to progression of left atrial structural remodeling due to deposition of collagen type III in patients with AF and mitral valve disease. Qian et al [110] reported a relationship between structural remodeling and persistent AF among patients with different type of mitral valve disease. They found different extent of interstitial fibrosis and ultrastructural alterations in AF patients with different types of mitral valve disease. In addition, authors found significantly higher amount of collagen type I and greater expression of MMP-2 in LAA from AF patients with mitral stenosis compared with LAA from AF patients with mitral regurgitation. Yongjun et al also found increased interstitial fibrosis in the LAA in patients with AF related to mitral valve disease, but contrary to Qian et al study, the interstitial fibrosis was more remarkable in mitral regurgitation group compared to mitral stenosis patients ($p < 0.05$) [111].

A role of mechanical stretch in collagen expression in atrial myocardium has been reported in previous studies [112]. A mechanical impact on cardiomyocytes increased collagen III/I ratio and did not influence the production of collagen type I levels, at least in vitro [112]. Recently, data on serum levels of the degradation products of collagen type I in patients with different clinical AF types and SR were published [113], showing that serum concentrations of a carboxy-terminal telopeptide of collagen type I was significantly higher in AF patients compared to those with SR, and concentration also differed between different clinical types of AF [113].

Boldt et al [109] did not found any association between the degree of atrial fibrosis and the atrial expression of the major extracellular matrix protein in different clinical AF types [109], means that fibrosis per se does not necessarily reflect atrial structural remodeling. As mentioned earlier, the mechanisms of AF

and atrial remodeling may differ in various clinical settings. Indeed, Zrenner et al performed multisite electrophysiologic mapping studies in the RA using basket catheter during paroxysmal and chronic AF, and concluded that in paroxysmal AF, the cycle length of arrhythmia is longer, and beyond reentry, there is focal activity [114].

Corradi et al evaluated myocyte changes and interstitial fibrosis in the LAA and left atrial posterior wall (LAPW) in 28 patients with chronic AF undergoing mitral valve surgery [115]. They found greater structural remodeling in the LAPW comparing with LAA, regardless of the type of mitral valve disease. In addition, signs of myocytes dedifferentiation were found using immunohistochemical analysis [115]. More recently, few studies reported histopathological changes in atrial tissue obtained from patients with valvular chronic AF undergoing cardiac surgery (Table 2) [116 – 118]. Castonguay et al found marked structural alterations in the appendages obtained from patients undergoing surgical Cox-maze procedure for AF treatment [119].

Moreover, Platonov et al reported a higher increase of interstitial fibrosis in atrial tissue in patients with permanent AF compared with those with paroxysmal AF [120].

Other example of atrial structural remodeling related to AF have been reported in other studies (Table 2). For example, Rőcken et al (97) examined RAA obtained from 245 patients undergoing cardiac surgery, and evaluated amyloid deposition by immunohistochemistry [97]. Amyloidosis is commonly observed in hearts of elderly people. The amyloid fibril protein consists of transthyretin and atrial natriuretic peptide in so-called “senile” cardiac amyloidosis. Amyloid which consists from atrial natriuretic peptide was found only in atrial myocardium of elderly human hearts and is called isolated atrial amyloidosis (IAA) [121]. However, IAA is not exclusive to elderly patients, as IAA has been detected in RA tissue obtained from 167 patients undergoing cardiac surgery, where the mean age of patients was only 39 years (range 25 to 52). In that study, IAA was

found mainly (88%) in patients with chronic rheumatic heart disease, and the presence of amyloid deposits in the RA was significantly higher ($p < 0.001$) [122]. However, these findings were not related to the presence of AF.

Theoretically, atrial amyloidosis may also disturb atrial conduction velocity and homogeneity by destroying cell-to-cell coupling and causing gap-junctional remodeling, which, in turn, increases the susceptibility to atrial arrhythmias. In their study, Rőcken et al [97] found that atrial deposits of amyloid were more frequently observed in patients with AF ($p < 0.01$). A reverse correlation between the amount of amyloid and fibrotic tissue in RAA was found ($p = 0.001$; $r = -0.55$), and fibrosis of RAA was not significantly associated with AF [97].

It is worth highlighting that most histopathological studies concerning the morphology of human atria have only evaluated RA tissue. However, it is known that the LA can be responsible for the initiation of AF [123]. The first work investigated the tissue specimens obtained from the both atria for the presence of IAA and related that finding to chronic valvular AF was published by Leone et al [124]. They showed that amyloid deposition (as confirmed by electron microscopy) was found in most (73%) specimens with IAA, as revealed using light microscopy, and the likelihood of amyloid deposition was greater in patients with a longer AF history ($p = 0.001$) [125].

In two studies, age did not correlate with the presence of IAA in patients with severe valvular heart disease [120, 124], suggesting that IAA is not just age related process, but was perhaps a pathophysiological response to the atrial pressure and volume overload. Although in these studies amyloid was not assessed for atrial natriuretic peptide, it is known from other studies that amyloid fibrils in IAA consist mainly of atrial natriuretic peptide [125], the synthesis of which increases by volume overload, tachycardia, ischemia and other factors [126]. Another recent paper described deposition of IAA in 100 hearts on autopsy [127] where the incidence of "senile" atrial amyloidosis increases with age and is more pronounced in females, consistent with previous studies [97, 124].

Table 2. Atrial histopathological abnormalities relating to atrial fibrillation

Author [reference]	Underlying heart disease associated with AF, n of patients	Tissue examined	Structural and ultrastructural abnormalities associated with AF
Frustaci et al. [108]	Lone AF N=12	Interatrial septum	Changes in 8 pts. corresponded to signs of myocarditis: foci of myocyte necrosis, infiltration of lymphocytes, interstitial fibrosis in 5 of them; In 2 pts.: Myocyte hypertrophy, vacuolization, focal interstitial fibrosis and on EM lysis of myofibrils, swollen mitochondria with fragmented cristae; In the last 2 pts.: Marked interstitial fibrosis
Boldt et al. [109]	Lone AF, valvular AF, controls N=118	LA biopsies	Marked interstitial fibrosis, myofibrils surrounded by connective tissue, myocytes separated by fibrotic fibrils The expression of collagen type III is markedly pronounced in the LA of patients with AF related to mitral valve disease.
Corradi et al. [115]	Chronic valvular AF N=28	LAA LAPW	Hypertrophy of myocytes, marked interstitial fibrosis, myocytes separated by connective tissue; on EM: perinuclear myolysis, which was more pronounced in the LAPW, thin, irregular myofilaments with widened Z bands in preserved sarcomers, accumulation of glycogen granules, elongated mitochondria with longitudinal orientation of cristae
Saito et al. [116]	Chronic valvular AF N=57 and 32 control autopsy cases	LAA	History of AF>10 y. associated with BN ($p<0.025$) and more extensive ICF ($p<0.05$); LA diameter – with enlarged nuclei ($p<0.05$), BN ($p<0.05$), extensive ICF ($p<0.05$), fatty infiltration ($p<0.025$); Higher PCWP – with more swollen nuclei ($p<0.05$), BN ($p<0.05$); Higher RAP – with hypertrophy ($p<0.05$), swollen nuclei ($p<0.05$), BN ($p<0.05$), extensive ICF ($p<0.05$); MS – hypertrophy ($p<0.025$), extensive ICF ($p<0.001$); Rheumatic valve disease vs. floppy MV: hypertrophy ($p=0.03$), larger nuclei ($p=0.009$), BN ($p=0.03$), extensive ICF ($p=0.001$), endocardial thickening ($p<0.006$); Floppy MV vs. controls: hypertrophy ($p=0.001$), larger nuclei ($p<0.0001$), BN ($p<0.0001$), more extensive ICF ($p<0.0001$).
Rőcken et al. [97]	Structural AF N=245	RAA	Deposition of amyloid, which was immunoreactive to atrial natriuretic peptide in 100% of cases, and in 10% - to transthyretine
Leone et al. [124]	Chronic valvular AF N=72	RAA LAA	Isolated atrial amyloid. On EM: amyloid fibrils in the myocardial interstitial space as typical thin, non-branching filaments.
Qian et al. [110]	AF related to MS or MR N=24	LAA	ICF in AF patients vs. SR group was more pronounced ($p=0.023$); AF related to MS vs. AF related to MR: extensive ICF ($p=0.043$), higher levels of collagen type I ($p=0.043$), intensive expression of MMP-2 ($p=0.001$). On EM: AF with MS: fibrotic bands; AF with MR: secondary lysosome-like bodies, myolytic areas with glycogen accumulation, abnormally shaped mitochondria, clumping of nuclei, and disruption of myofibrils.

Author [reference]	Underlying heart disease associated with AF, n of patients	Tissue examined	Structural and ultrastructural abnormalities associated with AF
Yongjun et al. [111]	AF related to MS or MR (N=24) and autopsy cases (N=4)	LAA	The average cross-sectional diameter of myocyte (μm) in MS+AF, MS+SR, MR+AF, MR+SR, and control group was 25.62±7.56, 20.20±9.34, 21.69±7.00, 13.93±4.32 and 9.81±2.34, respectively ($p<0.05$). ICF was more pronounced in AF cases compared with SR group ($p<0.05$), and ICF was greater in MR+AF vs. MS+AF ($p<0.05$).
Nguyen et al. [117]	MV surgery N=8 (chronic valvular AF N=5, SR N=3)	RAA Biopsies from PV-LA junction	AF vs. SR: lymphomononuclear infiltrate (100% vs. 33%, $p = 0.002$), ICF (37 ± 5.6% vs. 7.4 ± 2.8%, $p = 0.009$), greater sympathetic nerve twigs ($p = 0.03$).
Zhang et al. [118]	Chronic AF related to MV disease N = 12	RAA LAA	ICF was more pronounced in the AF group vs. SR group in both appendages: ICF in the LAA AF vs. SR $p=0.003$; ICF in the RAA AF vs. SR $p=0.017$.
Platonov et al. [120]	Autopsy cases without history of AF, with paroxysmal AF and permanent AF N = 30	Both atria	ICF and fatty infiltration were two- to threefold higher at all locations in AF group and correlated with lymphomononuclear infiltration. ICF in permanent AF group was greater than in paroxysmal AF group.
Castonguay et al. [119]	AF patients undergoing Cox-maze procedure (N=86) vs. autopsy cases as controls (N=45)	RAA LAA	Myocyte vacuolization, fatty infiltration, myocyte hypertrophy, ICF were more pronounced in appendages from AF group.

AF – atrial fibrillation, BN – bizarre nuclei shape, EM – electron microscopy, ICF – intercellular fibrosis, LA – left atrium, LAA – left atrial appendage, LAPW – left atrial posterior wall, MMP – matrix metalloproteinase, MR – mitral regurgitation, MS – mitral stenosis, MV – mitral valve, PCWP – pulmonary capillary wedge pressure, PV – pulmonary vein, RAA – right atrial appendage, RAP – right atrial pressure, SR – sinus rhythm. $P < 0.05$ considered as significant.

2.2.8. Histopathological data as a substrate for the development of postoperative atrial fibrillation

In 1999, Ad et al were the first to evaluate atrial histological abnormalities for predicting postoperative AF – they showed three histological findings in the RA myocardium as independent predictors for the development of postoperative AF, including size of myolytical vacuoles, vacuolation frequency and lipofuscin deposition [128]. In their subsequent publication of 60 patients undergoing elective

CABG [129], only severe myolysis in the RAA obtained before the commencement of cardiopulmonary bypass (CPB) independently correlated with the occurrence of postoperative AF (Table 3). Only one clinical factor – chronic obstructive pulmonary disease was detected as statistically significant prognostic factor for the development of AF ($p < 0.04$) following cardiac surgery. The authors did not detect any histological changes in RAA myocardium induced by ischemia or the cardiac surgery per se.

A later study conducted by Ak et al confirmed these results by detection of degree of myolysis as one of the predictors for the incidence of AF after the elective on-pump CABG in 100 patients [130]. Univariate analysis showed that not only myolysis but a greater apoptosis of myocytes as well are predictive histological factors for the occurrence of postoperative AF (Table 3). Older age did not correlate to the risk of postoperative AF in this study [130].

The presence of atrial structural remodeling prior to the cardiac surgery in patients with postoperative AF has been shown in studies with preoperative electrocardiographic abnormalities. A prolonged duration of P wave measured by signal-averaged ECG was found in patients developed postoperative AF [131-133] and echocardiographic studies [134] suggesting the existence of any structural atrial abnormalities would predispose to the slowing of conduction velocity in atria.

As mentioned above, atrial fibrosis results in conduction delay due to loss of cell-to-cell coupling and gap-junctional remodeling [Table 3]. Goette et al [135] first reported a correlation between intensity of right atrial fibrosis and P wave duration on the surface ECG, and both of them have been found independently predictive for development of AF following cardiac surgery. In addition, they determined significant correlations between fibrotic changes and age [135], perhaps due to replacement fibrosis due to myocyte loss [136] or reactive fibrosis induced by increased expression of TGF-beta [137].

Grammer et al evaluated RAA obtained from 33 consecutive patients undergoing cardiac surgery [138]. They established the expression of osteopontin mRNA (mitochondrial ribonucleic acid), ACE mRNA, and mRNA of collagen type III

and I, which were related to the development of postoperative AF. The amount of interstitial fibrosis in RAA did not differ in both groups, and only the decreased ratio of collagen type III/I was detected in postoperative AF group compared to the SR group. It is important to point out, that the size of this study is small, and patients underwent various cardiac surgery procedures [138].

Postoperative AF is more related to preoperative atrial structural abnormalities and on-pump CABG does not influence any additional histological changes in the RAA myocardium [Table 4]. In a prospective, randomized study of 70 patients randomized to on-pump elective CABG or off-pump, only vacuolisation of myocytes and their nuclear derangement were independent predictors of the occurrence of AF after the cardiac surgery, and not interstitial fibrosis or type of surgery [139]. Other studies also have not shown that off-pump CABG decreased the risk of postoperative AF [140 – 141], as was previously thought [142].

In contrast, other 'negative' studies are evident. For example, Cosgrave et al [143] assessed the RAA for 10 morphological features and did not revealed any histopathological correlations with development of postoperative AF. All the patients were followed-up for the development of postoperative AF just for 3 days in this study, and it may be possible that not all the cases of postoperative AF were taken into analysis.

Nakai et al [144] found that only advanced age was statistically significantly associated with RA fibrosis, and the degree of fibrotic tissue in the RAA tended to correlate with development of postoperative AF. In addition, Müller et al [145] found that more pronounced fibrosis in the RAA and total atrial conduction time were associated with the development of AF after cardiac surgery. Moreover, they reported that total atrial conduction time correlated with the degree of atrial fibrosis [145].

Recently, Kourliouros et al [146] reported that proteins associated with oxidative stress, apoptosis and acute phase response components were increased in LA of patients who had AF after elective CABG surgery (Table 4). Their finding consists with a study by Garcia et al [147] (Table 3).

Table 3. Studies in histologic preoperative atrial abnormalities related to the development of postoperative atrial fibrillation

Author [reference]	N of patients	Type of heart surgery	Tissue examined	Histological features associated with postoperative AF, (p value)	Clinical parameters associated with postoperative AF (p value)	Clinical parameters associated with histological abnormalities (p value)
Ad et al. [129]	N=60	Elective CABG	RAA	Lipofuscin deposition ($p<0.02$); Severity of myolysis ($p<0.02$)	COPD ($p<0.04$)	
Goette et al. [135]	N=259	Open heart surgery	RAA	The degree of fibrosis combined with P-wave duration ($p<0.01$)	Age >60 years ($p<0.05$); P wave duration ≥ 100 ms ($p<0.05$)	Age ($r=0.165$; $p<0.01$); P wave duration ≥ 100 ms ($r=0.249$; $p<0.01$)
Ak et al. [130]	N=100	Elective CABG	RAA	Larger size of myolytic vacuoles ($p=0.001$); Higher presence of apoptosis ($p=0.000$)	COPD ($p=0.014$)	
Grammer et al. [138]	N = 33	Elective CABG, CABG with AoVR, AoVR	RAA	Decreased collagen type III/I ratio in postoperative AF group ($p<0.05$)		
Mariscalco et al. [139]	N = 70	On-pump CABG; Off-pump CABG	RAA	Myocyte vacuoles ($p=0.002$); Nuclear derangement ($p=0.016$), fibrosis ($p=0.092$)	LA size ($p=0.008$); Requirement of inotropic agents ($p=0.001$)	Age > 65years – with fibrosis ($p<0.001$), fibroelastosis ($p=0.002$), hypertrophy ($p=0.01$); LA enlargement (.37 mm) – with nuclear derangement ($p=0.001$), fibrosis ($p=0.004$), myocyte vacuolization ($p=0.035$)

Author [reference]	N of patients	Type of heart surgery	Tissue examined	Histological features associated with postoperative AF, (p value)	Clinical parameters associated with postoperative AF (p value)	Clinical parameters associated with histological abnormalities (p value)
Cosgrave et al. [143]	N = 94	Elective CABG	RAA	Myolysis was more common in the postoperative AF group (p=0.745)		
Nakai et al. [144]	N = 61	Elective CABG	RAA	The amount of fibrosis (p=0.08, not statistically significant)	Greater age (p=0.017)	
Müller et al. [145]	N = 60 (histology N = 33)	Open heart surgery	RAA	Fibrosis extent was higher (p<0.001)	Total atrial conduction time was longer (p<0.001)	Total atrial conduction time correlated with degree of atrial fibrosis (r=0.73, p<0.01)
Kourliouros et al. [146]	N = 20	Elective CABG	LA	Peroxiredoxin 1, apoptosis inducing factor, 96S protease regulatory subunit 8, apolipoprotein A-I, fibrinogen were increased		
Garcia et al. [147]	N = 170	Elective CABG	RAA	Fibrosis, inflammation, myxoid degeneration, and ubiquitin aggregates did not differ. EM showed a significant accumulation of autophagic vesicles and lipofuscin deposits.	Serum C-reactive protein at baseline and 72 hours after the surgery did not differ	

AF – atrial fibrillation, AoVR – aortic valve replacement, CABG – coronary artery bypass grafting, COPD – chronic obstructive pulmonary disease, LA – left atrium, LAA – left atrial appendage, RAA – right atrial appendage, SD – standard deviation. P < 0.05 considered as significant.

Table 4. Inflammatory markers in peripheral blood for prediction of postoperative atrial fibrillation

Author, [reference]	N of patients, type of surgery	IL-6, postop. AF vs. no postop. AF	CRP, postop. AF vs. no postop. AF	Other inflammatory markers, postop. AF vs. no postop. AF
Fontes et al. [194]	N=72; cardiac surgery/on-pump	NS	Preoperatively: p=0.06	Increased of monocyte number after cross-clamp release (p=0.007); Increase in monocyte CD11b during surgery and immediately after (p=0.01); Increase in neutrophil count after cross-clamp release (p=0.005)
Hogue et al. [196]	N=141, women; cardiac surgery/on-pump	NS	Preoperatively: p=0.847 (did not differ significantly)	
Ahlsson et al. [197]	N=524, cardiac surgery/on-pump	NS	Postoperatively: p=0.99 (did not differ significantly)	
Ucar et al. [186]	N=49, CABG	Preoperatively: did not differ; Postoperatively (1st day): p<0.001	Preoperatively: p<0.005; Postoperatively (1st day): p<0.001	
Ishida et al. [187]	N=39; off-pump CABG	Following 3 h after anostomoses: p=0.0047; following 6 h after anostomoses: p=0.0005		TNF-alpha, CRP and IL-8 levels preoperatively, during surgery and postoperatively did not differ significantly
Lamm et al. [191]	N=253, cardiac surgery/on-pump			WBC count preoperatively: p=0.95; Postoperatively: p=0.048; Neither baseline, nor peak monocyte count differed; More pronounced increase in WBC count peak independently predicted AF
Pretorius et al. [198]	N=253, cardiac surgery/on-pump	Postoperatively: p=0.019; Preoperatively: p=0.098	Preoperative and postoperative levels did not differ significantly	Postoporatively: PAI-1 p=0.014; NT-proBNP: p=0.028; Preoperatively: PAI-1 p=0.044; Only preoperative PAI-1 (p=0.015) and postoperative PAI-1 (p=0.036) were independent predictors for postop. AF

Author, [reference]	N of patients, type of surgery	IL-6, postop. AF vs. no postop. AF	CRP, postop. AF vs. no postop. AF	Other inflammatory markers, postop. AF vs. no postop. AF
Lo et al. [185]	N=73 on-pump CABG; N=79 off-pump CABG		Preop: On-pump, p=0.01 Off-pump, p=0.002 (patients were divided in 'high' CRP level group based on cutoff value of >3.0 mg/L)	
Gaudino et al. [199]	N=110, CABG	Postoperatively: p<0.001	Postoperative levels did not differ (p=0.11)	The –174 C/G polymorphism of the promoter of the IL-6 gene associated with postoperative IL-6 levels and AF, p<0.001; postoperative levels of fibrinogen, p<0.001
Girerd et al [195]	N=2214 (male), on-pump CABG	NS	NS	Elevated waist circumference > 102 cm and CRP > 1.5 mg/L or IL-6 >2.2 pg/mL were associated with higher risk for postoperative AF (respectively, OR=2.32, p=0.02 and OR=2.27, p=0.03).
Ziabkhsh-Tabari S. [190]	N=54, on-pump CABG	Preoperatively p<0.05	NS	
Mirhosseini et al. [188]	N=104, off-pump CABG		Preoperatively, p=0.03	
Fontes et al. [192]	N=60, on-pump CABG		NS	A 2-fold higher preoperative white blood cell count was associated a nearly 7-fold higher risk of postoperative AF (p=0.01).
Kinoshita et al. [189]	N=683, off-pump CABG		Preoperatively, p=0.001	
Gibson et al. [193]	N=275, on-pump CABG		NS	A greater neutrophil/lymphocyte ratio preoperatively was associated with the development of postoperative AF (p=0.001).

Postop. AF – postoperative atrial fibrillation, CABG – coronary artery bypass grafting, CRP – C-reactive protein, IL – interleukin, NT-proBNP – N-terminal prohormone brain natriuretic peptide, PAI-1 – plasminogen activator inhibitor, TNF-alpha – tumor necrosis factor-alpha, WBC – white blood cel. P < 0.05 considered as significant.

2.2.9. The renin-angiotensin-aldosterone system and atrial remodeling

Substantial clinical data suggest that the RAAS is implicated in patophysiology of atrial remodeling, modulating AF development in relation to patients with hypertension, heart

failure, AF recurrence post-cardioversion or those post-myocardial infarction [148 – 149]. There are less clinical data on the role of RAAS in the occurrence of AF after cardiac surgery. The preoperative use of ACEI (angiotensin converting enzyme inhibitor) or ARB (angiotensin receptor blocker) in 338 patients undergoing cardiac surgery reduced the odds of the incidence in postoperative AF by 29%, but it did not reach the statistical significance, in a cohort study [150]. However, many published studies did not show that RAAS blockade significantly prevents the development of postoperative AF [151 – 153]. This is supported by extensive experimental data, which has examined the effect of the RAAS system on electrical atrial remodeling [154 – 156]. The RAAS might be activated in atria by atrial volume/pressure overload, given that a reduced density of angiotensin type 1 receptors and increased angiotensin type 2 receptors in fibrillating human atrial myocardium have been shown, thereby suggested promotion of fibrosis by stimulation of angiotensin type 1 receptors, which in turn, are downregulated [157] and linked to various mechanisms [158 – 163].

2.2.10. Oxidative stress

Cardiac surgery exacerbates the preexisting inflammatory process and cardiopulmonary bypass increases production of free radicals and exacerbation of oxidative stress, which may lead to the development of AF postoperatively [164]. In a small study of 24 patients undergoing CABG or valve surgery, there was significantly raised oxidative stress at 6 hours postoperatively as measured by peroxide levels and increased acute myocardial oxidation in the RA [165].

The impact of raised oxidative stress in AF has been studied in experimental [166] and human studies [167]. For example, atrial myofibril proteins are modified by oxidation significantly more in the AF group, causing dysfunction of myofibrils [168]. In addition, AF causes a decrease in nitric oxide (NO) production and a 1.8-fold increase in expression of plasminogen activator inhibitor-1 (PAI-1) in the LA endocardium, suggesting that oxidative stress is linked to endocardial dysfunction and thrombogenesis [169]. The increased activation of nicotinamide

adenine dinucleotide phosphate (NADPH) oxidase may be caused by angiotensin II via phosphorylation of p47phox [170]. Reactive oxidant species cause lipid peroxidation, breakdown of cell membrane, decreased mitochondrial function, calcium overload and apoptosis [171].

Oxidative stress plays a role in the development of postoperative AF as follows: reperfusion during CABG surgery results in oxidative stress [172], patients with postoperative AF have a larger increase in systemic and local (myocardial) oxidative stress [165], and finally, perioperative inflammation, but not the reperfusion injury, can stimulate atrial NADPH oxidase activity [173].

The implication of oxidative stress into pathophysiology of postoperative AF has been studied by administration of antioxidative drugs, and they were found attenuating the occurrence of AF after cardiac surgery [174 – 178]. It is well known, that the higher incidence of postoperative AF is in the elderly [10], and their hearts were established being more susceptible for ischemia/reperfusion injury [179].

2.2.11. Inflammation

There is a great interest into the role of inflammation in the pathogenesis of AF [19, 180]. For example, Frustaci et al [108] first demonstrated the presence of inflammatory changes in atrial tissue during the lone persistent AF. However, it remains unclear if AF causes inflammation, or a preexisting inflammatory process in atrial myocardium initiates structural atrial remodeling, and modulates AF promotion and maintenance. In addition, the precise role of inflammation in predicting AF after cardiac surgery is not well evaluated and there might be different structural and electrical substrate promoting the occurrence of arrhythmia. Recently, a preexistent elevated C-reactive protein was found associated with the recurrence of arrhythmia after catheter ablation of AF [181 – 182]. In an experimental animal study, the degree of atrial inflammation (index of infiltration by neutrophils, activity of myeloperoxidase) was associated with an increased inhomogeneity of atrial conduction and AF duration, and antiinflammatory

therapy significantly decreased this inhomogeneity in conduction and shortened the duration of AF [183]. Nonetheless, the early postoperative period after CABG is associated with a release of proinflammatory cytokines, but in one early study, this was not related to the development of post-surgery AF [184].

Other studies have suggested that inflammation did contribute to the development of AF after cardiac surgery [Table 4], for example, after the activation of complement system and the release of proinflammatory cytokines, given that the peak of arrhythmia events coincides with the highest CRP levels post-surgery [8]. Also high baseline CRP levels have been associated with a higher risk of AF development after both on-pump and off-pump CABG procedures [185 – 189]. There is only one small study that implicated higher preoperative IL-6 levels to the development of AF after CABG surgery [190]. A more pronounced postoperative elevation of white blood cell count and a greater neutrophil/leukocyte ratio were associated with the development of AF [191 – 193]. Perioperative monocyte CD11b upregulation, an increase in monocyte and neutrophils count obtained after aortic-cross-clamp release were reported in patients developed AF after on-pump cardiac surgery [194]. Recently, Girerd et al published a large (2214 male) study on postoperative AF, and concluded that patients with elevated waist circumference together with elevated CRP or IL-6 were at higher risk of the occurrence of postoperative AF [195]. Negative studies have also been reported [196 – 197]. In an interesting study by Pretorius et al [198], 21 biomarkers (different proinflammatory, prothrombotic and profibrotic indices) were measured in peripheral blood obtained preoperatively and immediately after CPB in 253 consecutive patients undergoing elective on-pump cardiac surgery, and PAI-1 – well known as an acute phase reactant – was the only independent predictor for the development of postsurgery AF [198].

It is unclear why the degree of postoperative inflammatory response differs between patients undergoing the same kind of heart surgery, and – as is well recognized – AF does not develop in 100% of them. Perhaps the existence of a

genetic predisposition to the inflammatory response to cardiac surgery leads to development of postoperative AF [199].

2.2.12. Extracellular matrix turnover

The matrix metalloproteinases (MMPs) are a family of enzymes that have a role in an extracellular matrix turnover and are involved into the degradation of interstitial and basement membrane collagens, proteoglycans and fibronectin, whilst their synthesis is induced after activation of cytokine, chemokine and growth factors [200]. The MMPs and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs) are also involved in the mediation of cell-to-cell adhesion, cell migration, invasion, proliferation and apoptosis and tissue remodeling, as well as the mediation of angiogenesis, cardiovascular development and diseases [201]. Importantly, there is an increasing body of evidence for MMPs and TIMPs in the pathogenesis of cardiovascular disease [202 – 203].

Increased a disintegrin and metalloproteinase (ADAMs) activity may be a molecular mechanism explaining structural remodeling in fibrillating human atria, leading to their dilation [94]. Indeed, Boixel et al report the MMP-7 is implicated into the development of LA fibrosis due to atrial overload in an animal experimental model [204]. The role of MMPs/TIMPs system in the atrial remodeling of fibrillating human atria in the setting of CHF is also recognized.

For example, Xu et al [205] examined atrial tissue samples from explanted 53 hearts of end-stage heart failure patients who underwent heart transplantation and 16 LA samples were taken as control from donor hearts. AF was documented prior to the transplantation in 37 patients (in 19 permanent AF and persistent AF in 18 of them), and downregulation of TIMP-2 ($p < 0.01$) and upregulation of MMP-2 ($p < 0.01$) was found in fibrillating atria (with more pronounced in the permanent AF group) compared to the controls. Moreover, they found a greater type I collagen volume fraction in the LA from AF patients, and the left atrial

type I collagen volume fraction was significantly correlated with the LA size and the TIMP-2 to MMP-2 ratio [93].

Differences in various MMP and TIMP levels between the four cardiac chambers, which are associated with altered collagen amounts have been shown [205]. In a study of 43 explanted hearts from end-stage CHF patients undergoing cardiac transplantation (23 were in AF), higher levels of MMP-1 in the RA and MMP-9 in the LA of AF group compared to the patients without history of AF ($p < 0.05$) were found. Collagen content was found greater in both fibrillating atria comparing with non-fibrillating atria ($p < 0.05$), and a linear correlation between AF duration and LA collagen amount was found ($r = 0.49$, $p = 0.023$). In addition, an inverse relation between soluble collagen I content and AF duration was identified ($r = -0.84$, $p = 0.036$) [205]. Greater expression of the active MMP-9 has been reported in the RAA obtained from patients with AF unrelated to CHF. For example, Nakano et al [27] examined 25 RAA excised from patients undergoing cardiac surgery (13 were in AF), and found a higher prevalence of the active form of MMP-9 in the RAA from AF patients ($p < 0.05$) using Western Blot analysis. In a study of RAA and LAA tissue samples collected during the mitral valve surgery (MVS) [206], there was an increased amount of fibrotic tissue and upregulated MMP-1 in the LA in MVS group, and in the RA of AF group. In contrast, MMP-9 was found downregulated in the both atria obtained from MVS group, regardless of the underlying rhythm, suggesting that AF per se does not contribute to the left atrial fibrosis and the induction of dysregulation of MMPs and the development of fibrosis were perhaps more likely to be due to hemodynamic overload [206]. Recently was demonstrated a pattern of MMP-9 influence on atrial remodeling in the setting of arterial hypertension [207], Corradi et al reported higher MMP-9 and MMP-2 levels in LA posterior wall in patients with valvular AF [208]. Huxley et al reported the prospective relationship between elevated levels of serum MMP-9 and risk of incident AF [209]. Case-control studies of genetic polymorphisms that alter

MMP-9 production and activity have also provided some support of a role of MMP-9 in the pathophysiology of AF [210 – 211]. Unfortunately, there is a lack of evidence concerning extracellular matrix turnover changes and its association with the incidence of AF after cardiac surgery.

2.2.13. Postoperative atrial fibrillation and prothrombotic state

Despite an increasing progress in technological advancements and the development of neuroprotective strategies in cardiac surgery, stroke and neurocognitive dysfunction remains a significant complication in this setting [212]. An incidence of adverse cerebral events of 6.1% has been reported following CABG surgery [212], leading to increased in-hospital mortality, worsened quality of life and increased healthcare costs [14, 212 – 214]. The association of AF with increased risk in cardiac thromboembolism has been well established and increasing evidence points towards the fulfillment of Virchow's triad for thrombus formation (thrombogenesis) in AF [215]. In the case of post-cardiac surgery AF, Virchow's triad also applies. Beyond individual patient characteristics (for example, as can be defined by CHA2DS2 – VASc stroke risk stratification scheme), the constant presence of structural heart disease, the surgery per se and CPB procedure, can all influence thrombogenesis.

2.2.13.1. Abnormal blood flow

With regard to 'abnormal blood flow', the absence of atrial systolic function during AF leads to intraatrial stasis, which increases yet more due to extremely shortened ventricular diastole in a case of tachysystolic AF, especially where structural heart disease with impaired ventricular filling preexists. Patients undergoing cardiac surgery usually present with significant structural heart disease, and, for example, hemodynamically significant mitral stenosis is associated with increased risk of thromboembolism due to stasis in the LA [216]. Moreover, temporary atrial mechanical dysfunction appears after restoration of

SR from AF, resulting in so-called 'atrial stunning' [217]. Duration of the latter condition depends on the duration of preceding AF, atrial diameter, underlying structural heart disease and the pathogenesis includes tachycardiomyopathy, atrial cytosolic calcium handling, oxidative stress, atrial hibernation with myocyte dedifferentiation and myolysis, as well as atrial fibrosis [218]. Intraatrial blood stasis can be visualized on the transesophageal echocardiography as spontaneous echocontrast, caused from interaction between red blood cells and fibrin where there is low blood flow [218]. Another echocardiographic parameter – decreased flow velocity in the LAA measured using Doppler technique has been associated with left atrial thrombus, spontaneous echocontrast and increased risk of thromboembolism [219].

2.2.13.2. Abnormal blood constituents

The second component of Virchow's triad is 'abnormal blood constituents', and this is evident by the vast literature showing abnormal platelets, clotting factors and fibrinolysis, in relation to AF. The vast majority of studies describe increased platelet activation in AF, although the magnitude may not be much more than that seen with associated vascular disease, which commonly coexists with AF [220 – 223]. Indeed, soluble P-selectin – an index of platelet activation – was not found associated with well known risk factors for thromboembolism in AF, except for diabetes mellitus [224], and neither was it predictive for stroke occurrence in a large cohort of nonvalvular AF patients [225]. Activated platelets during AF help promote extrinsic coagulation cascade and may lead to thrombogenesis and thromboembolism.

Recently, increased CD40 expression on the human RA endocardium and platelet-endocardial adhesion ($p < 0.01$ for both) were found associated with chronic AF compared to SR [226]. In an in vitro study using these tissue samples, simvastatin significantly reduced expression of CD40 and platelet adhesion to atrial endocardium [226]. As mentioned, many coagulation factors have been

found in nonvalvular AF patients, and intra-cardiac regional differences have been described. For example, higher levels of products of thrombin generation were found in the LA compared to the RA in patients presenting with mitral stenosis, whilst markers of platelet activity and fibrinolysis, and vWF did not differ between both atria [227]. However, this study was small and the findings were not related to AF, nor to the appearance of thrombotic changes within the LA. Boyaci et al reported increased regional left atrial coagulation and fibrinolytic activity, which was not reflective of levels in peripheral venous blood [228]. In contrast, Li-Saw-Hee et al did not determined any significant differences of prothrombotic markers and indices of endothelial dysfunction between peripheral arterial, venous blood and both atria in 25 patients with AF secondary to mitral stenosis [32] .

There are several reports indicating that degree of hypercoagulable state in AF depends on duration of arrhythmia [229 – 232]. Cardiac surgery and CPB are associated with increased activation of the hemostatic system per se. For example, thrombin generation is caused by the release of TF due to cutting of blood vessels, reinfusion of TF by return of cardiotomy suction blood during CPB [233], expression of TF on the surface of activated monocytes in the wound blood [234] and by the contact of blood with non-endothelial surface of CPB circuit [233]. It leads to the increase of fibrin formation, fibrinolysis and platelet activation [233, 235]. The activation of hemostasis has been established closely associated with the systemic inflammatory response after cardiac surgery with CPB [236].

Indeed, some investigators reported an excessive activation of hemostatic system during and early after cardiac surgery with CPB [237 – 239]. A small study by Hunt et al showed that CPB significantly increases activation of coagulation and fibrinolysis [237]. Casati et al described similar increase of D-dimers levels in both on-pump and off-pump groups in a non-randomized trial [238]. A paper by Lo et al [239] presents a comparison of hemostasis activation between on-pump and off-pump cardiac surgery patients, and found that coagulation and

fibrinolysis were more activated with on-pump surgery compared to the off-pump group. The peak of activation in hemostasis in the off-pump group was detected much later – after 20-96 hours following the operation [239].

2.2.13.3. Abnormal vessel wall

With regard to 'abnormal vessel wall', tissue trauma during cardiac surgery, as well as abnormal surface interactions during circulatory bypass can predispose to thrombogenesis. Atrial endocardial damage has been shown using scanning electron microscopy in patients undergoing MVS, which is most evident if AF is also present [240]. Another study by Masawa et al described areas of endothelial denudation and thrombotic aggregation in the LA on scanning electron microscopy in subjects (n = 31) who died from cerebral embolism, and these areas were observed significantly more frequent when history of AF was documented ($p < 0.001$) [241].

The presence of endocardial fibroelastosis and reduced area of transected pectinate muscle in LAA have been reported from chronic AF patients group (n = 22) as compared to that without AF (n = 24) [242]. These histological atrial abnormalities were related to blood stasis presenting in the LA during AF, but not to markers of endocardial damage, nor to blood hypercoagulability. Fukuchi et al. also reported endocardial overexpression of vWF in the LAA of patients with mitral valve disease independent of the presence of AF, and the grade of vWF expression significantly correlated with the degree of platelet adhesion/ thrombus formation in the endocardium [243]. Later, the authors examined atrial appendages excised from AF patients with or without structural heart disease, and found the association between increased endocardial vWF expression and enlargement of the LA or increased myocytes diameter in other underlying heart disease subjects, and fresh thrombi were co-localized with strong vWF staining [244]. These observations were more related to the associated structural heart disease, rather than to the existence of AF.

The implication of AF-related endocardial dysfunction might lead to the increased thrombogenicity was first suggested by Cai et al [169] in an experimental model with AF induced in pigs. The investigators detected decreased nitric oxide (NO) – distinguished for potent antithrombotic effects – production, downregulated NO synthase expression and increased expression of prothrombotic protein PAI-1, which is regulated by NO, by 1.8-fold in fibrillating animal left atria [169]. Later, the same group of investigators demonstrated an increase in superoxide production, particularly in the LA and LAA, as caused by AF induced in pigs [167]. Superoxide and reactive oxygen species themselves may activate factors of coagulation cascade in the endothelium [245].

Another animal study showed that rapid atrial pacing induces the downregulation of intrinsic anticoagulant factors – thrombomodulin and tissue factor pathway inhibitor – in the LA endocardium, but not in the ventricles [246]. In these animal models, AF per se is implicated as a cause of endocardial dysfunction that may lead to atrial thrombogenesis. Indeed, Nakamura et al [247] studied the LAA obtained from 7 patients with chronic AF and history of cardiac thromboembolic events, using histopatological and immunohistochemical methods, and found that the LA endocardia of all the 7 AF patients were infiltrated by inflammatory cells and samples were affected by persistent myocarditis.

In the study by Goldsmith et al [240], atrial endocardial surface changes in 35 mitral valve diseased patients were described using scanning electron microscopy and related to plasma levels of vWF. Ultrastructural changes of atrial endocardium were graded into 3 grades, and advanced changes were presented in the LAA (31% vs. 6%, $p = 0.00167$), whilst minimal changes were found in the RAA (23% vs. 6%, $p = 0.00167$). Endocardial damage was more evident if mitral valve stenosis or AF was present. Moreover, plasma vWf levels were higher in patients with mitral valve disease compared to healthy controls as well as in those with advanced LAA endocardiac alterations. The cndocardium could be considered as a part of endothelium, but how endothelial dysfunction/damage

and activation markers detectable in peripheral blood reflect their endocardial expression and structural abnormalities of the atrial endocardium, remains uncertain. A modest correlation between endothelial dysfunction markers (vWF, soluble thrombomodulin), fibrinogen and LA volume in 45 subjects with chronic nonvalvular AF has been reported, supporting a link between structural atrial remodeling and the prothrombotic state during chronic AF [248].

Inflammation may also 'drive' the prothrombotic state associated with AF. For example, the CRP and IL-6 single nucleotide polymorphism combination has been associated with the incidence of postoperative stroke in a prospective study of 2104 patients undergoing cardiac surgery, but these findings were not related to the correspondent plasma inflammatory and prothrombotic factors levels, nor to the occurrence of postoperative AF [249]. In contrast, other reports mentioned single-nucleotide polymorphism of CRP and IL-6 influences levels of their respective proteins in patients undergoing cardiac surgery [250 – 251]. Interestingly, there is an evidence of a genetic predisposition to inflammatory response related to cardiac surgery, which has been associated with the development of postoperative AF [199]. One large study has demonstrated increased expression of vascular cell adhesion molecule 1 (VCAM-1) in fibrillating atria and linked angiotensin II to the endocardial remodeling [252]. The investigators used tissue microarrays to assess RAA obtained from 320 patients undergoing cardiac surgery for evaluating the endocardial expression of VCAM-1, intracellular adhesion molecule 1, thrombomodulin, PAI-1 and vWF, and only VCAM-1 was expressed significantly more often in AF patients compared to those with SR. Moreover, atrial VCAM-1 expression and plasma angiotensin II levels increased after 7 hours of rapid atrial pacing in 14 pigs, particularly in the LA; treatment with ARB diminished the pacing-induced VCAM-1 expression in both atria. ARB decreased VCAM-1 upregulation also in ex vivo pacing model [252]. Recently, preoperative plasma VCAM-1 levels have been found predictive for the occurrence of postoperative AF in a cohort of 144 patients undergoing elective CABG surgery [253].

In conclusion, the pathophysiological processes that lead to the development of postoperative AF are closely inter-related. The most important ones that have bearing on preventive strategies include the RAAS, ion channels, connexins, fibrosis and extracellular matrix turnover, inflammation and oxidative stress. The autonomic nervous system and structural remodeling influence all these pathophysiological processes, which should not be viewed in isolation. Understanding such processes would have major implications for the approach to current preventive management.

2.3. Clinical features

Many patients with postoperative AF are asymptomatic [254] or present with complications resulting from AF. Others may experience palpitations, breathlessness, chest pain, excessive sweating or hypotension.

Most of arrhythmia episodes (76.8%) in the postoperative setting are diagnosed using continuous monitoring, and this figure is reduced to 17.5% by the use of 12-lead ECG for diagnosis and only 12.8% by physical examination [6]. Indeed, the 'pickup' rate for AF is much higher, if one looks harder for the arrhythmia. Many studies showed the presence of asymptomatic AF episodes that might be diagnosed with advanced methods of continuous ECG recording in different clinical settings [7, 254 – 263] (Table 5).

Many clinical variables are associated with the development of postoperative AF (Table 6). There is some controversy relating the impact of most of these features, and of the available data, only an advanced age has the strongest and most consistent evidence [1, 6 – 7, 10, 12, 18, 67, 134, 142, 264 – 300]. For example, prolonged aortic cross-clamp time, CPB time were found predictive for development of AF following cardiac surgery in a study by Almassi et al [1], but these factors were not significantly associated with postoperative AF in other work [6]. Electrocardiographic parameters are also not consistent between different studies (Table 7). Similarly, other clinical features as predictors for postoperative AF show a big heterogeneity between various studies or otherwise, scarcity of evidence exists.

Table 5. Asymptomatic atrial fibrillation and accuracy of diagnostic methods

Author, reference	Description
Kerr et al [255]	Prevalence of asymptomatic AF – 21%
Kopecky et al [256]	27 % of asymptomatic AF episodes in a population based study of lone AF
Page et al [257]	Routine transtelephonic ECG records revealed 17% of asymptomatic AF recurrences
Page et al [258]	Repeated 24-hour Holter ECG monitorings: asymptomatic AF episodes 12 times more frequent compared to symptomatic AF.
Schuchert et al [259]	72-hour Holter ECG monitoring was superior to 24-hour and 48-hour Holter ECG monitorings for detection of asymptomatic AF occurrences in patients after acute ischemic stroke
Flaker et al. [260]	481 (12%) patients had asymptomatic AF episodes, and they were more often men, had more cerebrovascular events, longer duration of AF, slower ventricular rate, better systolic LV function. Mortality and major events were similar for symptomatic and asymptomatic AF patients after 5 years.
Liao et al [261]	5 trials with Holter ECG monitoring for patients after ischemic stroke (n=588) – revealed 4.6% of new AF. 2 trials used event loop recorders for AF detection in patients after ischemic stroke (n=140): new AF was diagnosed in 5.7% and 7.7%.
Roche et al [262]	Negative 24-hour Holter ECG monitoring followed by automatic long-term event recorder revealed 31% of AF occurrences (55% of them were asymptomatic)
Defaye et al [263]	Data retrieved from pacemaker's memory showed 21% of asymptomatic AF episodes in patients without previous history of arrhythmia.
Landymore et al. [254]	Asymptomatic AF episodes (54%) on 24-hour Holter ECG monitor at discharge and after 3 weeks after cardiac surgery (10%)

AF – atrial fibrillation, ECG – electrocardiogram, LV – left ventricular.

Table 6. Pre-, intra- and postoperative clinical risk factors associated with atrial fibrillation following cardiac surgery

Preoperative risk factors
Advanced age [1, 6 – 7, 10, 12, 18, 264 – 267]
Male gender [10]
Hypertension [1, 6, 10]
Previous AF [6, 267]
History of cardiac surgery [265]
CHF [6]
COPD [6, 12, 18, 264]
RCA disease [289]
Peripheral vascular disease [12]

Preoperative risk factors
Echocardiographic parameters [6, 265, 269, 277 – 288]
Electrocardiographic features [264, 267 – 276]
Renal failure [142, 266]
Moderate or severe aortic atherosclerosis [6]
Withdrawal beta-blocker or ACEI [6]
BSA [267, 277]
Obesity and metabolic syndrome [292 – 295]
RDW [296]
BNP [297 – 299]
Intraoperative risk factors
Aortic cross-clamp time [1]
Bicaval canulation [6]
Pulmonary vein venting [264]
Type of surgery [6 – 7, 264 – 265]
Need of perioperative IABCP [10, 12]
CPB time [1, 282]
CPB inclusive of cardioplegic arrest [142]
Systemic hypothermia [265]
Postoperative risk factors
Respiratory compromise [10]
Red cell transfusion [132]
Higher TnI levels [300]

ACEI – angiotensin converting enzyme inhibitor, AF – atrial fibrillation, BNP – brain natriuretic peptide, BSA – body surface area, CHF – congestive heart failure, COPD – chronic obstructive pulmonary disease, CPB – cardiopulmonary bypass, IABCP – intra-aortic balloon counterpulsation, LVH – left ventricular hypertrophy, RCA – right coronary artery, RDW – red cell distribution width, TnI – troponin I.

2.3.1. Electrocardiographic and echocardiographic parameters associated with the development of atrial fibrillation following cardiac surgery

The role of preoperative ECG changes for prediction of AF following cardiac surgery has been investigated in many studies (Table 7).

The duration of P wave reflects atrial conduction, and consequently, many studies have investigated the prognostic value of this parameter on incidence of AF, particularly after successful cardioversion [133, 268]. In contrast to study by Chandy et al [267], other studies have found that the duration of P wave measured preoperatively by signal average ECG was a significant predictive marker for postoperative AF [131 – 133] (Table 7). In a small study of 95 patients, Hayashida et al [269] found that signal-averaged P wave duration together with older age and left atrial enlargement were independent predictors for AF following cardiac surgery (Table 7).

Chandy et al [267] also evaluated the ECGs of 300 patients without history of AF preoperatively and after CABG surgery, and found that only increased dispersion of P wave measured postoperatively compared with preoperative measurements (odds ratio (OR) = 1.13, 95% confidence interval (CI) 1.01-1.05). In this study, the duration of P wave was not associated with development of AF after CABG. Other studies (Table 7) have also reported that the signal-average ECG was not useful for predicting postoperative AF [270 – 272].

Dispersion of the P wave is an indirect marker of atrial refractoriness. The significance of dispersion in atrial refractoriness for maintenance of AF has been shown in animal experimental models [273] and clinical studies [267, 274]. The chance of reentry generation increases when the atrial depolarizing impulse interferes with areas of heterogeneous refractoriness, resulting in fragmentation of the propagating impulse. The prognostic value of dispersion of atrial refractoriness in the development of postoperative AF has been described in various electrophysiological studies [275]. However, the mechanisms and causality of postoperative dispersion of atrial refractory period are unclear, but may relate to atrial volume overload or ischemia. The study by Chandy et al [267] did not find any electrographic signs of ischaemia immediately prior to onset of postoperative AF. Recently, magnesium has been reported to diminish postoperative occurrence of P wave dispersion [276].

In their study of 300 patients, Chandy et al investigated electrocardiographic signs of pericarditis in eight subjects, and only two experienced postoperative AF [267].

A study by Leung et al [277] investigated the relation of preoperative and postoperative echocardiographic parameters (Table 7) on the occurrence of postoperative AF (as detected by continuous telemonitoring during their full hospitalization period) in 300 patients undergoing elective CABG surgery. Larger LA area and lower LA ejection fraction (EF) preoperatively were associated with the occurrence of postoperative AF on univariate analysis. Multivariate

analysis showed that predictors for the postoperative AF development were the following: greater age, body surface area, white race, a lower atrial filling fraction postoperatively and a left ventricular (LV) diastolic dysfunction postoperatively [277] (Table 7). This study showed that patients with an increased risk for the incidence of postoperative AF have architecturally and functionally abnormal and remodeled LA prior to the heart surgery.

Other earlier and more controversial works on echocardiographic parameters as predictors for the development of postoperative AF involved smaller number of patients [278] (Table 7). For example, Tsang et al [279] reported that diastolic LV dysfunction and its severity were independent predictors for the development of future non-valvular AF. Recently, Melduni et al [280] showed that abnormal LV diastolic dysfunction was predictive for the development of postoperative AF (Table 7). Benedetto et al [281] used tissue Doppler imaging techniques to show that patients with an increased risk for the development of postoperative AF had functionaly abnormal LA preoperatively (Table 7). In contrast, Nakai et al [282] reported that LA volume – but not LA function – was predictive for the occurrence of AF following cardiac surgery (Table 7). This is consistent with the study by Osranek et al [283], which showed that LA volume assessed preoperatively is associated with the occurrence of postoperative AF in a study of 205 patients undergoing cardiac surgery (Table 7). Recent study by Haffajee et al [284] showed an impaired LA mechanical function as a predictor for the development of postoperative AF (Table 7). Also some studies reported LA strain and strain rate measured by speckle tracking associated with the occurrence of postoperative AF [285 – 287] (Table 7).

Roshanali et al (Table 7) described a new echocardiographic parameter – an atrial electromechanical interval measured using tissue Doppler echocardiography – for the prediction of AF following CABG, which had 100% sensitivity and 94.8% specificity [134]. They speculated that prolonged atrial electromechanical interval in patients, who develop postoperative AF, might be explained by LA

enlargement and atrial conduction delay [134]. More recently, other studies confirmed predictive value of atrial conduction time measured by tissue Doppler imaging for postoperative AF [67, 288] (Table 7).

The overall incidence of postoperative AF depends on arrhythmia recording method with the best diagnostic value using continuous ECG monitoring techniques. Advanced age has been shown the best predictive clinical factor, whereas other features, including ECG and echocardiographic parameters are lack a high specificity and positive prediction value.

Table 7. Studies on electrocardiographic and echocardiographic parameters for prediction of postoperative atrial fibrillation

Author, reference, number of patients, type of surgery	ECG parameters	Results	Echocardiographic parameters	Results
Steinberg et al [131], n = 130, cardiac surgery	fPWD on the SAECG preoperatively	fPWD > 140 ms predicted POAF (sensitivity of 77%, specificity of 55%, negative predictive value of 87%, positive – of 37%)		
Caravelli et al [132], n = 129, CABG	fPWD on the SAECG preoperatively; RMSV10; RMSV20	fPWD ≥ 135 ms predicted POAF (sensitivity of 84%, specificity of 73%, negative predictive value of 85%, positive – of 70%). Smaller RMSV10 ($p<0.001$) and RMSV20 ($p<0.001$) in POAF group		
Aytemir et al [133], n = 53, CABG	fPWD on the SAECG preoperatively	fPWD > 122.3 ms predicted POAF (sensitivity of 68%, specificity of 88%, negative predictive value of 83%, positive – of 76%)	LV EF; LA posteroanterior diameter	NS
Hayashida et al [269], n = 95, CABG or AoVR	fPWD on the SAECG preoperatively	fPWD ≥ 135 ms predicted POAF ($p=0.02$; OR 3.5)	LA diameter	Larger LA diameter in POAF patients ($p=0.003$)

Author, reference, number of patients, type of surgery	ECG parameters	Results	Echocardiographic parameters	Results
Budeus et al [289], n = 101, CABG	fPWD on the SAECG preoperatively. RMSV20	fPWD ≥ 124 ms predicted postop. AF (sensitivity of 78%, specificity of 75%, negative predictive value of 86%, positive – of 64%). Smaller RMSV20 (p<0.0001) in POAF group		
Gang et al [270], n = 151, CABG	fPWD on the SAECG preoperatively. P wave morphology dispersion	NS		
Chandy et al [267], n = 300, CABG	P wave characteristics pre- and postoperatively	Larger decrease in postoperative P wave duration in POAF group (p<0.0001). Larger increase in postoperative P wave dispersion in the POAF group (p=0.028)		
Dogan et al [272], n = 57, CABG	P wave dispersion on the surface 12-lead ECG preoperatively	Longer P wave dispersion was associated with POAF (55.0±8.2 vs. 41.3±14.3 ms, p=0.008)		
Stafford et al [290], n = 201, CABG	fPWD on the SAECG preoperatively	fPWD > 141 ms predicted POAF (negative predictive value of 83%, positive – of 34%)	LA diameter	NS
Amar et al [271], n = 250, thoracic surgery	fPWD on the SAECG preoperatively	NS		
Hashemi Jazi et al [272], n = 52, CABG	PWD pre- and postoperatively	PWD pre- and postoperatively was longer in POAF group (p<0.005)	LV EF, mitral regurgitation, regional wall motion abnormalities	The mean LV EF was lower in POAF group (p<0.005)
Açil et al [278], n = 102, CABG			LA diameter	LA diameter predicted the POAF (p=0.047)

Author, reference, number of patients, type of surgery	ECG parameters	Results	Echocardiographic parameters	Results
Osranek et al [283], n = 205, cardiac surgery			LAV, LV EF, LV diastolic function	Larger AF in POAF group (p=0.0001)
Benedetto et al [281], n = 96, CABG			LA area, peak atrial systolic mitral annulus velocity	Larger LA area in POAF group (p=0.007), lower peak atrial systolic mitral annulus velocity (p=0.01)
Nakai et al [282], n = 93, CABG			LA area, LA finction	Larger LA area in POAF group (p<0.001), lower atrial index (p=0.008)
Leung et al [277], n = 300, CABG			LA area, LAA area, LA EF, LAA EF, LV EF, LA length, LAA peak velocity, VTI of E/A, E/A, E duration, atrial filling fraction, peak A velocity, hepatic vein diameter and velocity, pulmonary vein haemodynamics and diameter. All measurments were done pre- and postoperatively.	Preoperatively: larger LA area (p=0.0092), lower LA EF (p=0.027) in POAF group. Postoperatively: atrial filling fraction ≤ 0.36 (p=0.04) and E duration ≥ 270 ms (p=0.0067) increased risk of POAF.
Roshanali et al [134], n = 355, CABG			LV EF, max. transmitral A wave Doppler flow velocity, LAV, atrial EMI	Lower LV EF, reduced max. transmitral A wave Doppler flow velocity, increased LAV, prolonged atrial EMI in POAF group.
Melduni et al [280], n = 351, cardiac surgery			LV diastolic function	Rate of POAF increased exponentially with LV diastolic finction grade severity (p<0.001)
Haffajee et al [284], n = 101, cardiac surgery			Max. LAV, min. LAV, LA TEF	LA TEF was lower in POAF group compared with SR group (43±15% vs. 55±13%, p<0.001)

Author, reference, number of patients, type of surgery	ECG parameters	Results	Echocardiographic parameters	Results
Gabrielli et al [285], n = 70, CABG			LA strain and strain rate measured by speckle tracking	LA strain s wave and LA strain rate s, and wave a were significantly decreased in POAF group (p<0.001)
Levy et al [286], n = 58, AoVR			Complete baseline echocardiography, including global and segmental longitudinal strain using 2D speckle tracking	Parameters associated with POAF: aortic valve area (p=0.04), E/E' ratio (p=0.04), global longitudinal strain (p=0.005)
Her et al [287], n = 53, CABG			Complete baseline echocardiography, including global and segmental longitudinal strain using 2D speckle tracking	Parameters associated with POAF: larger LAV index (p=0.018), lower value of LA global strain (p=0.001) and atrain rate (p=0.024)
Ozlü et al [288], n = 128, CABG			PA-TDI duration	Increased PA-TDI duration in POAF group (134.3±19.7 vs. 112.5±17.7 ms, p=0.01)
Müller et al [67], n = 60, cardiac surgery			PA-TDI duration	Increased PA-TDI duration in POAF group (152.1±30 vs. 120.8±1.8 ms, p<0.001)

AoVR – aortic valve replacement, CABG – coronary artery bypass grafting, ECG – electrocardiogram, EF – ejection fraction, EMI – electromechanical interval, fPWD – filtered P wave duration, LA – left atrial, LAA – left atrial appendage, LAV – left atrial volume, LV – left ventricular, NS – no significance, PA-TDI – total atrial conduction time measured by tissue Doppler imaging, POAF – postoperative atrial fibrillation, PWD – P wave duration, SAECG – signal averaged electrocardiogram, RMSV10 – root mean square voltage of the last 10 ms of atrial depolarization, RMSV20 – root mean square voltage of the last 20 ms of atrial depolarization, VTI – velocity time integral, TEF – total emptying fraction. P < 0.05 considered as significant.

2.4. Preventive strategies with antiarrhythmic drugs and interventions for postoperative atrial fibrillation

Given that postoperative AF is a major clinical problem, antiarrhythmic drugs have been used to prevent this arrhythmia (Table 8). In a meta-analysis, Zimmer

et al reported that prophylactic treatment for decrease postoperative AF reduced hospital length stay and costs, but did not significantly affect stroke and mortality [301]. A further analysis by Burgess et al [302] evaluated 29 trials and found that the benefit of preventive strategies for shortening of hospital stay for postop AF was only associated with amiodarone (OR – 0.60 95% CI –0.92 to –0.29) and pacing (OR – 1.3 95% CI –2.55 to –0.08). Also, only amiodarone had significant impact on reducing postoperative stroke incidence (OR 0.54, 95% CI 0.30 – 0.95) [302].

2.4.1. Beta-blockers

Andrews et al published the first meta-analysis showing the beneficial effects of beta-blocker therapy in suppression of postoperative AF (34% vs. 8.7%, $p < 0.0001$) [5]. A large meta-analysis by Crystal et al determined the benefit of beta-blocker pretreatment and continuation postoperatively on reduction of postsurgery AF (33% vs. 19%) with a huge heterogeneity between trials ($p < 0.00001$); there was no relation to type of beta-blocker, regimen or pretreatment and trial size [303]. A further meta-analysis of 31 randomized controlled trials (RCTs) [302] showed broadly similar benefits for beta-blockers. In studies in which beta-blocker was withdrawn at the time of surgery there was a much higher effect in the treatment group (OR 0.30, 95%CI 0.22 – 0.40) compared to trials with continuation of non-study beta-blocker in control group (OR 0.69, 95%CI 0.54 – 0.87); this suggests significant heterogeneity between different studies and perhaps an underestimation of the preventive effects associated with beta-blockers [302]. Ali et al showed that a rebound fenomenon due to beta-blockers withdrawal before the surgery caused a two-fold increase in the incidence of postoperative AF, suggesting a benefit of continuity of preoperative beta-blocker therapy after cardiac surgery in prevention of postoperative AF [304]. Therefore, guidelines recommend oral beta-blocker therapy should be started at least 1 week before the cardiac surgery [305].

Halonen et al reported that intravenous metoprolol started early postsurgery was well tolerated and superior to oral administration against postoperative AF, perhaps due to diminished absorption from gastrointestinal tract very early after cardiopulmonary perfusion [306]. Also, the preoperative use of beta-blocker reduced perioperative mortality from 3.4% to 2.8% (OR 0.8; 95%CI 0.78 – 0.82), [307]. More recent metaanalysis of 118 studies with 138 treatment groups showed high efficacy of beta-blockers and sotalol in the prevention of the incidence of AF after cardiac surgery [308]. Unsurprisingly, the American Heart Association guidelines strongly recommend preoperative or early postoperative beta-blocker therapy for patients undergoing CABG [309]. The European Association for Cardio-Thoracic Surgery guidelines recommends beta-blockers as first choice for the prevention of postoperative AF in all the patients undergoing cardiac surgery, unless they are contraindicated [310].

However, the optimal beta-blocking agent has not been defined yet for prevention of postoperative AF. Iliuta et al reported a superiority of betaxolol therapy compared with metoprolol in reducing of various complications after cardiac surgery [311]. It is well known that carvedilol beyond its extensive sympatholytic effect carries antioxidative properties [312]. Several prospective randomized trials showed an advantage of carvedilol over metaprolol for the prevention of postoperative AF [313 – 315].

Recently, a novel intravenous beta-blocker landiolol was shown highly effective in prevention of postoperative AF [316 – 317].

2.4.2. Sotalol

Seven randomized studies comparing efficacy of sotalol to conventional beta-blocker treatment in prevention of postoperative AF were described by Patel and Dunning [79]. Five of the seven studies showed statistically significant advantage of sotalol over beta-blocker in reduction of postoperative AF, and two other investigations did not show a significant benefit of sotalol [318]. Several trials

used sotalol preoperatively 40 mg tds or 80 mg bd continuing postoperatively, and this regimen was not associated with increase of side effects [319]. A meta-analysis of four trials (sotalol vs. beta-blocker against postoperative AF) revealed that sotalol is more effective than beta-bloker and number needed to treat with sotalol over beta-blockers was 10 [303]. Similar results were shown by Burgess et al in their meta-analysis of seven RCTs and by Kerin and Jakob [302, 320]. Recent meta-anlysis of 118 trials reported similar effect of sotalol and beta-blockers in postoperative AF prophylaxis [308].

2.4.3. Amiodarone

Amiodarone is efficacious in prophylaxis of postoperative AF compared with controls in large meta-analyses of RCTs, although there is a wide variety in dose, duration of treatment and routes of delivery [302 – 303, 308]. The AFIST II trial showed a benefit of combined intravenous and oral amiodarone use starting early postoperatively compared to placebo: postoperative AF occurred in 22.1% vs. 38.6% of patients, respectively; $p = 0.037$ [319]. There is also a beneficial effect of combined intravenous and oral amiodarone treatment in reduction of AF after CABG in high-risk patients identified using P-wave signal average ECG [321].

The largest trial of amiodarone for the prevention of postoperative AF – PAPABEAR – was published in 2005, and reported that oral amiodarone use for 13 days perioperatively was an effective and safe approach in AF prophylaxis after cardiac surgery, even in a specific subgroup of patients with perioperative use of beta-blockers (15.3% vs. 25.1%, $p = 0.03$, in favour of amiodarone), although this trial is somewhat unpowered concerning safety [322]. A recent meta-analysis of 14 RCTs ($n = 2864$) aimed to clarify an optimal dose and time of amiodarone prophylaxis for AF following cardiac surgery [323] found no significant difference on postoperative AF suppression between low dose (defined as less than 3000 mg), medium (3000 – 5000 mg) or high (more than 5000 mg) ($p = 0.238$), and no significant difference between preoperative vs. postoperative

starting time of amiodarone (p = 0.862) [323]. A prospective randomized study by Beaulieu et al did not confirm the effect of intravenous perioperative amiodarone use for postoperative AF prevention, moreover, AF occurred more frequently in amiodarone group compared with placebo (59.3 vs. 40.0%, p = 0.035) [324]. More recently, a large meta-analysis of 23 studies analysed the route of delivery and timing of prophylactic administration of amiodarone [325]. The meta-analysis revealed that a regimen of both oral and intravenous administration, as well pre- and post-operative prescription of amiodarone is effective for prevention of AF after cardiac surgery [325]. The European Association for Cardio-Thoracic Surgery guidelines recommends amiodarone for the prevention of postoperative AF in all patients undergoing cardiac surgery when beta-blockers are contraindicated (Grade A recommendation based on level 1a and 1b studies) [310].

2.4.4. Magnesium

Magnesium is highly effective in the reduction of postoperative AF. Magnesium is a cofactor of Na-K adenosine triphosphatase, which regulates the myocardial transmembrane sodium and potassium gradients [326] and decreased levels of magnesium postoperatively are associated with a higher risk of AF occurrence after cardiac surgery [60]. The large meta-analysis by Shiga et al determined that magnesium is superior to traditional antiarrhythmic therapy in the prevention of postcardiac surgery AF: the numbers needed to treat for magnesium are 13, which are lower compared to traditional antiarrhythmics (beta-blocker – 7, sotalol – 5, amiodarone – 7) [327].

Burgess et al also found a similar overall reduction of postoperative AF by magnesium in their meta-analysis of 22 trials with various dosing strategy, time of delivery and significant heterogeneity (p < 0.001) [302]. Similar results showed Alghamdi et al [328]. Recent meta-analysis by Gu et al reported that intravenous magnesium reduced the incidence of postoperative AF by 36% with no heterogeneity between trials (heterogeneity p = 0.8, I2 = 0%) [329].

Thereby, magnesium is simple, well-tolerated and cost-effective drug to prevent AF after cardiac surgery.

2.4.5. Other antiarrhythmic drugs

Digoxin does not show any benefit for postoperative AF prophylaxis (OR 0.97; 95% CI 0.62 – 1.49) [330].

A subgroup analysis in a meta-analysis of calcium channel blockers found that non-dihidropyridines significantly suppressed postsurgery supraventricular arrhythmias (OR 0.62 95% CI 0.41 – 0.93), but with high heterogeneity ($p = 0.03$) [331].

A double-blind, placebo-controlled randomized trial by Serafimovski et al showed effective and safe use of dofetilide for prophylaxis of AF after CABG [332].

Ito et al reported that propaphenone hydrochloride is effective in prevention of postoperative AF compared with control ($p = 0.0337$), but the administration of the agent should be carefully considered individually [333].

A few studies evaluated the efficacy and safety of procainamide use in postoperative AF prophylaxis, and data are controversial regarding this issue [334 – 335].

An antianginal agent ranalozine also prolongs atrial refractoriness and inhibits triggered activity. Recently, it was found to be more effective than amiodaron preventing postoperative AF [336], but randomized studies are needed to confirm these results.

2.4.6. Temporary pacing

Studies on overdrive temporary pacing for postoperative AF prevention are small in size, with different pacing protocols. Published meta-analyses show that only bi-atrial pacing have an advantage in AF suppression after the cardiac surgery compared to controls, and especially combined with oral beta-blockers

[302 – 303, 308]. However, biatrial pacing is limited in practice because of its complexity.

With reference to recommendations of the European Association for Cardio-Thoracic Surgery guidelines, bi-atrial pacing significantly decreases the occurrence of postoperative AF [310].

2.5. Non-antiarrhythmic drug approaches for the prevention of postoperative atrial fibrillation

2.5.1. The impact of the renin-angiotensin-aldosterone system inhibition

The RAAS has been implicated in pathophysiology of atrial remodeling. Thus, substantial clinical data on RAAS blockade by the ACEI and ARB on modulating AF has accumulated [337].

Pedersen et al [149] first reported that ACEI use reduce the number of AF episodes in patients with LV dysfunction after myocardial infarction. Since then, a large number of retrospective studies and meta-analyses have examined the influence of RAAS inhibition on the development of AF in different settings in humans, with studies in CHF [338], in arterial hypertension with LV hypertrophy [339], and after an acute myocardial infarction with systolic LV dysfunction [149].

A meta-analysis of 9 large, randomized studies with RAAS blockade showed the overall decrease in number of new-onset AF by 18%, especially in CHF setting (by 43%) [340]. In an analysis from the CHARM trial (candesartan vs. placebo in CHF patients with secondary end-point of new-onset AF) enrolled 6379 patients with SR on baseline ECG. Candesartan significantly decreased development of new-onset AF in this particular patient population [341]. Based on a meta-analysis of four large trials, Kalus et al [342] reported that inhibition of RAAS prevented the development of new-onset AF, improved the likelihood of SR restoration after electrical cardioversion, and decreased the number of AF recurrences after successful cardioversion.

Indeed, the positive role of RAAS suppression on AF recurrences has been demonstrated in some prospective trials [343 – 344], even in combination with antiarrhythmic drugs. One prospective, double-blind, placebo-controlled trial of 171 patients with persistent AF did not reveal any benefit of candesartan on recurrences of AF after successful electrical cardioversion during 6 months follow-up period [345].

Other small prospective studies did not find any significant positive effect of RAAS inhibition on the relapses of AF after successful cardioversion [346 – 347]. The GISSI-AF trial – prospective, randomized, placebo-controlled, multicenter study of 1442 patients – did not prove the effect of the ARB valsartan on SR maintenance after successful cardioversion [348].

Should an ACEI or ARB be used to prevent AF post-cardiac surgery? In experimental work, there was positive effect of ARB candesartan in the prevention of structural atrial remodeling and atrial endocardial dysfunction, at least in hypertensive rats [349].

Trials in post-cardiac surgery per se are limited. One retrospective single centre analysis showed that ACEI or ARB use did not significantly prevent the development of postoperative AF [151], although there was a reduction in the odds of postoperative AF by 29% [150]. One small study of 128 patients showed a beneficial effect of ACEI and ARB on the occurrence of AF after cardiac surgery [350]. Unfortunately, later studies did not find any protective effect of RAAS blockade on the development of postoperative AF [153, 351 – 353]. Rader et al did not reveal any significant reduction of postoperative AF by angiotensin blocking drug therapy in a large retrospective observational study of 10552 partipiciants [351]. Chin et al did not show any preventive effect of RAAS blockade on the occurrence of postoperative AF, but they found that ACEI or ARB administration was rather associated with an increased incidence of AF after off-pump CABG surgery [352]. Recently, Pretorius et al reported in their randomized controlled trial of 445 patients that neither ACEI nor

mineralcorticoid receptor blockade decreased the incidence of AF after cardiac surgery [153]. More large prospective trials are needed to clarify the true effect of RAAS inhibition on the development of postoperative AF.

2.5.2. 3-hydroxy-3-methyl-glutaryl coenzyme A inhibitors

A few studies have examined the use of statins in relation to the development of post-op AF. The antiarrhythmic mechanism of statins can be explained by their effects on inflammation [354 – 357], antioxidant effects [358 – 359], antiarrhythmic effects due to ion channel stabilization [360], a role in extracellular matrix modulation [361], an inhibition of synthesis of isoprenoids that are significant for the posttranslational modification of such signaling molecules as Rho, Rac, and Ras [359], and an ability to reverse angiotensin II mediated atrial structural remodeling [362].

Many studies on statins are nonrandomized and are based on registry analysis. For example, Marin et al reported significant decrease in incidences of AF after elective CABG when patients were on statin therapy prior to surgery [361]. However, the study was retrospective, included patients with previous history of AF, and various statin pretreatment regiments were used and a number of subjects is too small to conclude exact effect of statins on reduction of postoperative AF. A retrospective analysis [363] on statin and postoperative AF among patients (included from prospective randomized Atrial Fibrillation Suppression Trials I, II, and III) receiving prophylactic beta-blocker and amiodarone treatment showed that adjunctive statin pretreatment suppressed postoperative AF by 40% [363]. Furthermore, Ozaydin et al reported that pretreatment with statins was protective against the development of AF after CABG (on Kaplan-Meier analysis $p = 0.01$), but also shortened the duration of postoperative AF episodes ($p = 0.0001$) [364]. A few meta-analyses showed not only a beneficial effect of pretreatment with statins on the development of postoperative AF, but also their advantage in shortening of total hospital stay [365 – 366]. The advantage of

statin pretreatment in the suppression of AF incidence after elective CABG may not depend on type, dose or duration of use [365, 367].

Nonetheless, negative studies showing no benefit of statins on postop AF also exist. For example, pretreatment with statin prior to cardiac surgery did not show any significant benefit for reducing the risk in the development of postoperative AF [368]. However, this study was conducted retrospectively, and patients received different statins, variable doses were used and there were incomplete data on the duration of statin treatment prior to cardiac surgery [368].

The first randomized, placebo-controlled trial on statin pretreatment for reduction of postoperative AF incidences was the ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmia after cardiac surgery) trial [354], which showed a significant decrease in postoperative AF occurrences after pretreatment with atorvastatin. Moreover, hospital length stay was shorter in the atorvastatin group compared to placebo ($p = 0.001$). The investigators related development of postoperative AF and use of statin to plasma CRP levels measured dynamically, and found significantly higher postoperative peak CRP levels in AF patients compared to those remained in SR ($p = 0.01$) [354]. However, the ARMYDA-3 trial did not found any statistical association between statin use and levels of plasma CRP [354].

A few large retrospective studies showed a decreased mortality and morbidity in patients treated with statin before cardiac surgery, although this effect was not statistically significant in a subgroup of subjects after valve surgery [369 – 370]. Pretreatment with statin prior to elective CABG surgery showed significant decrease in perioperative mortality in a large, retrospective study [371] and in an analysis from a large, prospective, longitudinal, multicenter McSPI (the MultiCenter Study of Perioperative Ischemia) trial, a significant reduction of early cardiac death (OR 0.25; 95% CI 0.07 – 0.87, $p < 0.03$) after CABG [372]. Thus, pretreatment with statin seems to be useful particularly prior to the CABG surgery, despite the small incidences of rhabdomyolysis caused by high doses

of statin [373]. A recently published meta-analysis of 6 randomized studies on impact of statin treatment in suppression of AF included 2 studies with postcardiac surgery AF. Based on this meta-analysis, the authors concluded that statins are more beneficial in secondary AF prevention, rather in primary prevention, and their effect does not appear to be related to dose [374]. Contrarily, Mithani et al showed a dose dependent effect of statins on AF after cardiac surgery [375].

Statins appear to be underutilized for patients undergoing cardiac surgery, particularly for those undergoing CABG, and it is seems to be due to their perioperative safety. However, the benefits seem to outweigh the risks associated with statin use. Future studies are needed to reveal the optimal perioperative statin regimen.

2.5.3. n-3 polyunsaturated fatty acids

The n-3 polyunsaturated fatty acids (PUFAs) are distinctive due to their antiarrhythmic effect on fatal ventricular arrhythmias [376], and high plasma concentrations of PUFAs caused by fish consumption have been found associated with lower incidence of AF during 12 years period [377].

In a prospective, randomized, controlled trial, pretreatment with PUFAs decreased the development of AF after CABG surgery and shortens hospital length stay [378]. However, the present single-centre study was not double blinded, and postoperative AF monitoring was not performed continuously in all patients. A study by Mariscalco et al showed that preoperative administration of PUFAs reduced the early occurrence of postoperative AF, but did not prevent from late AF [379]. Of note, the study was limited by its lack of randomization. There was a big expectancy in antifibrillatory effect of PUFAs among cardiac surgery patients. Unfortunately, further randomized controlled trials did not prove this hypothesis. A meta-analysis of four RCTs did not find any association between PUFAs use and the reduction in postoperative AF [380]. More recently, a large (n = 1516) double-blind, placebo-controlled, randomized clinical trial showed

tha perioperative fish oil consumption had no beneficial effect on th incidence of AF following cardiac surgery [381].

2.5.4. Antiinflammatory drugs

Corticosteroids are well known antiinflammatory agents, and inflammation has been proposed in the pathogenesis of AF post-cardiac surgery. One prospective, randomized, double-blind trial of intravenous corticosteroids administration in suppression of postoperative AF has been published [382]. This study found a significant risk reduction of postoperative AF in those treated with hydrocortisone group compared to placebo, and when this study was included in a meta-analysis with two previous, there was a reduction of postoperative AF [382]. A few meta-analyses of randomized, controlled trials again suggested an effect of perioperative corticosteroid use on AF occurrence, on length of stay in the intensive care unit and total hospital stay after cardiac surgery, with an overall benefit of treatment with corticosteroids concerning all end-points [383 – 385]. Of note, the use of steroids was not associated with an increased risk of infectious complications [385]. In addition, a few prospective, randomized, controlled studies demonstrated the advantage of corticosteroid use before CABG surgery in reducing incidence of postoperative AF, although this was not a primary end-point of those trials [386 – 387].

However, a randomized, double-blind study on the effects of corticosteroids on development of AF after combined valve and CABG surgery did not revealed any differences between treatment and placebo groups on the dynamic release of plasma proinflammatory markers, but this was based on a small number of patients (n = 78) [388].

A positive impact of suppression of inflammatory process on the development of postoperative AF has also been shown using non-steroidal antiinflammatory drugs [389]. However, this study did not reveal any significant increase in stroke or myocardial infarction development after cardiac surgery [389], and the study

was not prospective, randomized and controlled, and it probably underpowered concerning safety. Recently, a randomized, controlled study did not find any reduction in the incidence of postoperative AF by naproxen compared with placebo ($p = 0.11$), but the study agent significantly decreased the duration of AF episodes ($p = 0.04$) [390]. Of note, the trial was stopped because of an increase in renal failure in the naproxen group.

Recently, an old anti-inflammatory agent colchicine was studied for prevention of postoperative AF, and was found significantly effective in reducing the incidence of AF following cardiac surgery [391].

Anglade et al demonstrated that the preoperative use of thiazolidinedione, which has some antiinflammatory properties, in diabetic patients undergoing cardiac surgery was associated with 20% reduction in postoperative AF – however, it did not reach statistical significance due to being underpowered [392].

2.5.5. Miscellaneous

Oxidative stress has been implicated into pathogenesis of AF, and there are some studies tested antioxidative agents for suppression of postoperative AF. Indeed, the possible beneficial effects of vitamin C [174] and N-acetylcysteine [175 – 176] have been suggested in this setting. However, recent prospective, double-blinde, placebo-controlled, randomized study by Kazemi et al did not prove the benefit of N-acetylcysteine administration for prevention of postoperative AF [393].

Sodium nitroprusside – a nitric oxide donor – other promising agent for the prevention of postoperative AF. Cavolli et al reported that sodium nitroprusside significantly reduced the incidence of postoperative AF compared to placebo ($p = 0.005$) [178]. However, contrary evidence exists concerning preventive features of sodium nitroprusside against postoperative AF [394].

The American College of Chest Physicians (ACCP) guidelines recommends mild hypothermia (for example, 34 oC), the use of posterior pericardiotomy and heparin-coated CPB circuits as intraoperative preventive strategies for reduction

of AF following cardiac surgery [395]. There is some contradictory evidence concerning the advantage of off-pump CABG over conventional CABG with CPB in reducing the rate of postoperative AF. Some meta-analyses showed that off-pump CABG significantly lower incidence of postoperative AF compared to on-pump [396 – 397] but the metaanalysis by Burgess et al did not found a high heterogeneity ($p < 0.001$) and a lack of studies with postoperative AF as a primary end-point [302]. Turk et al reported a prospective study of off-pump CABG vs. on-pump CABG on the occurrence of postoperative AF, and did not found any significant difference between these operative techniques in the preventive strategy for preventing postoperative AF [141].

Despite some hopeful preliminary results of the ventral cardiac denervation by retention of anterior pericardial fat pad for prevention of postoperative AF [80], the AFIST III trial ($n = 180$) did not find any significant benefit of such an intervention [398].

In conclusion, with regard to preventive options – only beta-blockers and amiodarone have shown a potent effect on the suppression of AF postoperatively. The role of other drugs, such as RAAS blockers (ACEI, ARBs) and statins in modulating the incidence of postoperative AF merits further study.

Table 8. Preventive strategies for postoperative atrial fibrillation

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
Zimmer et al, 2003, [301]	Meta-analysis: 13 RCTs, n=1783	Various antiarrhythmics and atrial pacing	CABG, valve or both/on-pump		OR 0.52, 95% CI 0.41-0.65	Shortening of length of stay by 1 day+/-0.2; Mean reduction in costs of $1287+/-$673;
Andrews et al, 1991, [5]	Meta-analysis: 24 RCT, blinded and open:		CABG			
	1) N=1549 (13 trials);	1) Various beta-blockers;			1) OR 0.28 95% CI 0.21-0.36;	
	2) n=507;	2) digoxin in a various dose regimen;			2) OR 0.97 95% CI 0.62-1.49;	
	3) n= 432	3) verapamil in a various dose regimen			3) OR 0.91 95% CI 0.57-1.46;	
Crystal et al, 2002, [303]	Meta-analysis: 1) 27 RCT, n=3840;	1) Various beta-blockers;	CABG, valve or both/on-pump		1) OR 0.39, 95% CI 0.28-0.52; NNT = 7;	Second-points – length of stay and stroke reduction -NS
	2) 8 RCT, n=1294;	2) sotalol;			2) OR 0.35, 95% CI 0.26-0.49;	
	3) 9 RCT, N=1384;	3) amiodarone;			3) OR 0.48, 95% CI 0.37-0.61;	
	4) 4 RCT, N=900;	4) sotalol vs. other beta-blocker;			4) OR 0.50, 95% CI 0.34-0.74;	
	5) 10 RCT, a)N=581;	5) pacing: a) RA;			a) OR 0.68, 95% CI 0.39-1.19;	

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
	b)N=148;	b) LA;			b) OR 0.57, 95% CI 0.28-1.16;	
	c)N=744	c) Bi-atrial			c) OR 0.46, 95% CI 0.30-0.71	
Halonen et al, 2006, [306]	RCT, N=240	I/v metoprolol 1-3mg/h vs. oral metoprolol 25 mg tpd or 50 mg bd for 48 hours started early postoperatively	CABG, valve or both/on-pump	Continuous ECG monitoring for 48 hours or until the first AF episode	i/v metoprolol vs. oral: 16.8% vs. 28.1%, respectively, p=0.036	
Burgess et al, 2006, [302]	Meta-analysis: 1)31 RCT, N=4452;	1) Beta-blocker;	CABG, valve or both/on-pump		1) OR 0.36, 95% CI 0.28-0.47;	
	2) 7 RCTs, N=1240;	2) Sotalol vs. beta-blcker;			2) OR 0.42, 95% CI 0.26-0.65;	
	3) 18 RCTs, N=3295;	3) Amiodarone;			3) OR 0.48, 95% CI 0.40-0.57;	
	4) 22 RCTs, N=2896;	4) Magnesium;			4) OR 0.57, 95% CI 0.42-0.77;	
	5) 14 RCTs, N=1885:	5) Overdrive pacing			5) OR 0.60, 95% CI 0.47-0.77	
	a) 9 RCTs, N=723;	a) RA;			a) OR 0.74, 95% CI 0.48-1.12;	
	b) 4 RCTs, N=408;	b) LA;			b) OR 0.70, 95% CI 0.46-1.07;	
	c) 10 RCTs, N=754	c) Bi-atrial pacing			c) OR 0.44, 95% CI 0.31-0.64	
Arsenault et al, 2013, [308]	Meta-analysis 118 RCTs N=17364	1) Beta-blockers	Cardiac surgery		1) OR 0.33, 95%CI 0.26-0.43	
		2) Sotalol			2) OR 0.34, 95%CI 0.26-0.43	

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
		3) Amiodarone			3) OR 0.43, 95%CI 0.34-0.54	
		4) Magnesium			4) OR 0.55, 95%CI 0.41-0.73	
		5) Atrial pacing			5) OR 0.47, 95%CI 0.36-0.61	
		6) Posterior pericardiotomy			6) OR 0.35, 95%CI 0.18-0.67	
Budeus et al, 2006, [321]	RCT, double-blind, pacebo controlled, N=110	Combined i/v and oral amiodarone starting 1 day before and continuing to 7 day after surgery	CABG	Follow-up – for 7 days by Holter monitoring	OR 0.91, 95% CI 0.036-0.235	
Mitchell et al, 2005, [322]	PAPA-BEAR RCT, double-blind, placebo controlled, N=601	Oral amiodarone 10 mg/kg for 13 days starting 6 days prior to surgery	CABG, valve or both/on-pump	Follow-up with continuous monitoring for 6 days	OR 0.52, 95% CI 0.34-0.69	
Shiga et al, 2004, [327]	Meta-analysis: 17 RCTs, N=2069	Magnesium	CABG, valve or both/on-pump		OR 0.77, 95% CI 0.63-0.93, p=0.002; NNT=13	No significant effect on hospital stay and postoperative MI
Gu et al, 2012, [329]	Meta-analysis: 7 RCTs, N=1028	Intravenous magnesium	CABG		OR 0.64, 95%CI 0.50-0.83, p=0.001	
Serafimovski et al, 2008, [332]	Prospective, randomized, double-blind, placebo-controlled. N=133	Dofetilide vs. placebo	CABG	Continuous monitoring	Absolute RR 18%, p<0.017; NNT = 5.4	
Reston et al, 2003, [397]	Meta-analysis: 28 RCTs and cohort studies	Off-pump CABG vs. on-pump CABG	CABG, off-/on-pump		OR 0.69, 95% CI 0.58-0.81	

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
Raja et al, 2004, [398]	Meta-analysis: 6 RCTs, N=1262	Off-pump CABG vs. on-pump CABG	CABG, off-/on-pump		OR 0.77, 95% CI 0.62-0.95; NNT=20	
Turk et al, 2007, [141]	Prospective, case-matched study, N=267	Off-pump CABG vs. on-pump CABG	CABG, off-/on-pump	Continuous monitoring during the first 72 hours	No significant difference	
Caló et al, 2005, [378]	RCT, placebo controlled, N=160	PUFAs, 2g/day, 5 days prior to surgery and continued until discharge	Elective CABG	Continuous monitoring for the first 4 to 5 days, then 12-lead ECG every day until discharge	Absolute risk reduction 18.1%, relative risk reduction – 54.4%; NNT 5.51	Shorter hospital length stay (p=0.017)
Mariscalco et al, 2010, [379]	Retrospective, N=530	PUFAs	Cardiac surgery		OR 0.54, 95%CI 0.31-0.92 for early AF incidence	
Armaganijan et al, 2011, [380]	Meta-analysis: 4 RCTs, N=538	PUFAs	Cardiac surgery		OR 0.79, 95%CI 0.56-1.13, p=0.195	
Mazaffarian et al, 2012, [381]	OPERA: prospective, double-blind, placebo-controlled, randomized study. N=1516	PUFAs	Cardiac surgery		No difference in postoperative AF (p=0.74).	
Marin et al, 2006, [361]	Retrospective, cross-sectional, N=234	statin	CABG/ on-pump		OR 0.52, 95% CI 0.28-0.96, p=0.038	
Patti et al, 2006, [354]	AR-MYDA-3 Prospective, randomized, placebo controlled, single-centre, N=200	Atorvastatin 40mg for 7 days prior to surgery	CABG, valve or both/on-pump	Continuous telemonitoring for at least 6 days	OR 0.39, 95% CI 0.18-0.85, p=0.017	

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
Lertsburapa et al, 2008, [363]	A nested cohort study from AFIST I, II and III trials, N=555	statin	CABG, valve or both/on-pump	Continuous telemonitoring	OR 0.60, 95% CI 0.37-0.99	
Mariscalco et al, 2007, [367]	Retrospective, longitudinal, observational, N=405	Statin	Elective CABG		OR 0.58, 95% CI 0.37-0.91, p=0.017	
Ozaydin et al, 2007, [364]	Observational, N=362	Statin	CABG		Protective impact by Kaplan-Meier analysis (p=0.01)	Less frequency (p=0.03) and duration of AF episodes (p=0.0001)
Virani et al, 2008, [368]	Retrospective, single-centre, N=4044: 2096 with pretreatment and 1948 without	Statin (various statins, doses and regimens)	CABG, valve or both/on-pump	Continuous telemetry during hospitalization period	OR1.13, 95% CI 0.98-1.31, p=0.08 No significane, even after propensity score analysis (OR 1.14, 95% CI 0.92-1.41, p=0.21)	
Fauchier et al, 2008, [374]	Meta-analysis: 6 RCTs, 2 of them – on postoperative AF, N=3557	Statin	CABG		OR 0.60, 95% CI 0.27-1.37 (for primary prevention and postoperative AF); Overall: OR 0.39, 95% CI 0.18-0.85	
Mithani et al, 2009, [375]	Retrospective, N=1936	Simvastatin	Cardiac surgery		>20 mg daily had 36% reduction of postoperative AF (OR 0.64, 95%CI 0.43-0.60, p=0.03)	

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
Chen et al, 2010, [365]	Meta-analysis: 8 RCTs, N=774	Statin	Cardiac surgery		OR 0.57, 95%CI 0.45-0.72, p<0.0001	Reduced total hospital stay (p=0.0004).
Girerd et al, 2012, [370]	Retrospective. N=6728	Statin	CABG		OR 0.38, p=0.003	Reduced long-term mortality (follow-up 6 years, p=0.03)
Liakopoulos et al, 2012, [366]	Meta-analysis: 11 RCTs, N=984	Statin	Cardiac surgery		OR 0.40, 95%CI 0.29-0.55, p<0.01	
Halonen et al, 2007, [382]	Prospective, randomized, double-blind, placebo controlled, multicenter, N=241	Hydrocortisone i/v 100 mg on the operative day followed by 100 mg every 8 hours for the next 3 days	CABG, valve or both/on-pump	Continuous ECG recording during the first 84 hours after surgery	OR 0.63, 95% CI 0.45-0.87; p=0.003	CRP levels in treatment group were significantly lower on the first, second and the third postoperative days compared to placebo group (p=0.02, p<0.001, p<0.001, respectively)
Halonen et al, 2007, [382]	Meta-analysis: 3 RCTs, N=621	Corticosteroids	CABG, valve or both/on-pump		OR 0.67, 95% CI 0.54-0.84, p=0.001	
Baker et al, 2007, [383]	Meta-analysis: 9 RCTs , N=990	Corticosteroids	CABG, valve or both/on-pump		OR 0.55, 95% CI 0.39-0.78	Hospital length stay shortening by 1.6 day
Whitlock et al, 2008, [384]	Meta-analysis: 44 RCTs, N=3205	Cortocosteroids	Cardiac surgery		OR 0.71, 95%CI 0.59-0.87, p=0.001	Reduced postoperative bleeding (p<0.0001), duration of ICU stay (p=0.006) and total hospital stay (p=0.04)

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
Ho et al, 2009, [385]	Meta-analysis: 50 RCTs, N=3323	Corticosteroids	Cardiac surgery		OR 0.74, 95%CI 0.63-0.86, p<0.01; NNT, 10.	Reduced length of stay in the ICU (p<0.01)band hospital stay (p=0.03).
Imazio et al, 2011, [391]	Multicenter, double-blind, placebo-controlled, randomized trial. N=336	Colchicine	Cardiac surgery		RR 45%, NNT, 11.	Shorter total hospital stay (p=0.04)
Ruffin et al, 2008, [389]	A nested cohort study from AFIST I, II and III, N=555	NSAIDs	CABG, valve or both/on-pump		OR 0.54, 95% CI 0.32-0.90	Reduced need for red blood cell transfusion (by 37%); No increase in stroke or MI incidence
Horbach et al, 2011, [390]	RCT, N=161	Naproxen vs. placebo	CABG	Continuous monitoring	NS	
Gu et al, 2012, [176]	Meta-analysis: 8 RCTs, N=578	N-acetylcysteine	Cardiac surgery		OR 0.62, 95%CI 0.41-0.93, p=0.021	No effect on hospital stay (p=0.7)
Kazemi et al, 2013, [393]	Prospective, double-blind, placebo-controlled, randomized study. N=240	N-acetylcysteine vs. placebo	Cardiac surgery	Continuous monitoring	NS	
Cavolli et al, 2008, [178]	Prospective, randomized, placebo-controlled. N=100	Sodium nitroprusside	CABG	Continuous monitoring	The occurrence of AF was lower in treatment group (p=0.005)	
Bolesta et al, 2012, [394]	Retrospective, observational. N=1025	Sodium nitroprusside	Cardiac surgery		NS	

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
Mathew et al, 2004, [6]	Retrospective, observational study from 70 centers, N=4657	Perioperative ACEI	CABG, valve or both/on-pump		OR 0.62, 95% CI 0.48-0.79	
White et al, 2007, [150]	A nested cohort study from AFIST I, II and III, N=338	Preoperative ACEI or ARB	CABG, valve or both/on-pump		OR 0.71, 95% CI 0.42-1.20	
Coleman et al, 2007, [151]	Retrospective cohort analysis, N=1469	Short-term use of ACEI or ARB postoperatively	CABG, valve or both/on-pump		OR 0.95, 95% CI 0.57-1.56	
Ozaydin et al, 2008, [350]	RCT, N=128	ACEI or ARB vs. control	Cardiac surgery		AF: control gr. vs. ACEI gr. (33.3% vs. 12%, p=0.02); control gr. vs. ACEI and ARB gr. (33.3% vs. 10.2%, p=0.01)	
Rader et al, 2010, [351]	Retrospective, N=10552	ACEI or ARB	Cardiac surgery		OR 1.05, 95%CI 0.96-1.16, p=0.38	
Pretorius et al, 2012, [153]	Randomized, double-blind, placebo-controlled. N=445	Ramipril, spironolactone, placebo	Cardiac surgery		Neither ACEI, nor spironolactone decreased the postoperative AF (p=0.95)	
Chin et al, 2012, [352]	Retrospective, observational. N=1050	ACEI or ARB	Off-pump CABG		NS	
Anglade et al, 2007, [392]	A nested cohort study from AFIST I, II and III, N=184	Thiazolidinedione (patients with beta-blocker and amiodarone)	CABG, valve or both/on-pump		OR 0.80, 95% CI 0.32-1.99	

Author, year of publication, [reference]	Design, n of subjects	Treatment studied	Type of cardiac surgery	Arrhythmia recording	Reduction of postoperative AF in treatment group	Other variables, associated with treatment
Omran et al, 2010, [83]	RCT, N=220	Ventral cardiac denervation	CABG		Ventral cardiac denervation was predictive for the incidence of AF (p=0.044)	

ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin II type 1 receptors blocker, AF – atrial fibrillation, CABG – coronary artery bypass grafting, CI – confidence interval, CRP – C-reactive protein, ECG – electrocardiogram, i/v – intravenous, MI – myocardial infarction, NNT – numbers needed to treat, OR – odds ratio, PUFAs – n-3 pollyunsaturated fatty acids, NSAIDs – non-steroidal antiinflammatory drugs, RCT – randomized controlled trial. $P < 0.05$ considered as significant.

3. METHODS

3.1. Patient's characteristic, cardiac surgery technique and follow-up

One hundred four consecutive patients (mean age 64.2 ± 8.9 years, 15 female and 89 male) undergoing primary elective on-pump CABG surgery for clinical need at Vilnius University Hospital Santariskiu Klinikos were recruited into the prospective, cross-sectional study between October 2006 and May 2007. The inclusion criteria were: patients scheduled for elective on-pump CABG surgery, aged older than 18 years. Exclusion criteria involved any history of AF, pacemakers, previous cardiac surgery, any cancer, any chronic inflammatory disease, significant liver failure (an increase in transaminase activation more than three times), significant renal failure (serum creatinine concentration above 200 μmol/L), any hematologic disease, moderate - severe valvular disease, any acute cerebrovascular event or an acute inflammatory disorder within 60 days prior to the operation, treatment with steroids in the previous 6 months. Patients were enrolled into the study after signing their written informed consent. The study was approved by the Lithuanian Bioethics Committee (Reference number – 2, issued on the 3rd of February 2006).

All the patients underwent medical history recording, physical examination, coronary angiography, transthoracic echocardiography, 12-lead ECG recording, routine hematological and biochemical blood tests prior to the surgical intervention. All patients received beta-blockers preoperatively and this was continued following cardiac surgery.

CABG was performed by identical surgical and anesthetic protocols for each patient. The induction of anesthesia was performed with midazolam, fentanyl, and etomidate. Recuronium or cisatracurium were used for myorelaxation. A mixture of volatile anesthetics, benzodiazepines and opioids was used to maintain the anesthesia. Cardiopulmonary bypass was proceeded with ascending aortic and two-stage venous cannulation of the RA at systemic mild hypothermia

(32 – 34 oC). The extracorporeal circuit was primed with 1000 ml of Ringer's lactate, 500 ml of hydroxyethylstarch 130/0.4 6%, 250 ml of mannitol 15% and 1.0 g of cefazolin. Non-pulsatile pump flow was kept between 2.0 – 2.4 L/min/m2 to maintain mean arterial pressure between 50 and 70 mmHg. Hydroxyethylstarch 130/0.4 6% and gelatine 4% were used for volume therapy during and after cardiac surgery. The activated clotting time (ACT) was kept above 480 seconds with unfractionated heparin during an artificial blood circulation period. Myocardial protection was accomplished by means of antegrade and retrograde intermittent cold blood cardioplegia. The left internal thoracic artery was routinely grafted to the left anterior descending artery, whereas the saphenous vein was used for other target coronary arteries. Following the cessation of the cardiopulmonary bypass, heparin was neutralized with protamine sulfate to correct the ACT to less than 120 seconds. After the operation all the patients were monitored in the Intensive Care Unit (ICU) for at least 24 hours.

Continuous ECG monitoring was performed only in the ICU following by routine 12-lead ECG recording every morning or in case of clinical symptoms or irregular pulse at physical examination during all hospitalization period. All the patients were discharged to the rehabilitation clinic and followed-up for AF occurrence until the 30th postoperative day. Postoperative AF was defined as any electrocardiographically documented AF episode lasting more than 30 seconds. Clinical data were prospectively recorded and tabulated with Microsoft Excel (Microsoft Corp., Redmond, Wash).

3.2. Blood collection and analysis

Ten milliliters of citrate blood samples were obtained from 5 different sites of each patient. Peripheral venous blood was taken just before the CABG surgery. A direct venepuncture was performed in the morning on patients who had been fasting for > 12 hours and had rested for at least 20 minutes. Blood samples from the RA, RAA and LA were obtained immediately after the pericardiotomy,

and from the LAA – after commencement to the CPB circuit. All blood samples were drawn atraumatically and without stasis into vacuum tubes preloaded with trisodium citrate (0.011 mol/L), mixed by gentle inversion and stored on melting ice. Plateled-poor plasma fractions were separated by centrifugation within 15 minutes of collection (at 2500 rpm for 15 min at 4oC). Plasma aliquots were stored at minus 70oC until use. Plasma aliquots (preserved by dry ice) were transported to Birmingham, UK. Research indices were assayed in the Haemostasis, Thrombosis and Vascular Biology Unit, City Hospital, Birmingham, UK. Researches were blinded to the patient's clinical details.

Plasma vWF, TF, IL-6, MMP-9 and TIMP-1 were measured by ELISA (enzyme-linked immunosorbent assay) using commercially available reagents. The unit for vWF is IU/dL and was standardized on the ground of vWF from the National Institute for Biological Standards and Controls, other biomarkers (units: pg/mL) were standardized by the recombinant product supplied by the manufacturer. Intra-assay coefficients of variations for all assays were < 5%, inter-assay coefficients of variations were < 10%. Plasma hs-CRP levels (mg/L) were measured using a latex-enhanced immunonephelometric assay.

3.2.1. Tissue factor ELISA assay

Plasma TF was measured by ELISA using commercially available reagent AssayMax Human Tissue Factor (Assaypro LLC, St. Charles, Missouri, USA). All plasma samples were brought to room temperature and diluted 1:2 into MIX Diluent (a 10-fold concentrated buffered protein base). All reagents were diluted and brought to room temperature before use. 400 pg of TF Standard (lyophilized human recombinant TF in a buffered protein base) was reconstituted with 0.1 ml of MIX Diluent to generate a 400 pg/ml of solution. Triplicate standard points were prepared by serially diluting standard solution twofold with equal volume of MIX Diluent to produce 200, 100, 50, 25, 12.5 pg/ml. MIX Diluent served as the zero standard (0 pg/ml). The assay was performed at room temperature

(20-30 °C). 96-well polystyrene microplates (12 strips of 8 wells) coated with a polyclonal antibody against TF were used for the assay. Fifty µl of standard or sample was added per well, then wells were incubated for two hours. After two hours, wells were washed five times with 200 µl of Wash Buffer (buffered surfactant). Microplates were inverted, hit five times on absorbent paper towel to complete liquid removing. Fifty µl of Biotinylated TF Antibody (biotinylated polyclonal antibody against TF) was added to each well; plates were incubated for one hour and then washed five times with 200 µl of Wash Buffer as above. Fifty µl of Streptavidin-Peroxidase Conjugate was added to each well; microplates were incubated for 30 minutes and washed five times with 200 µl of Wash Buffer as above. Fifty µl of Chromogen Substrate (stabilized peroxidase chromogen substrate tetramethylbenzidine) per well was added and incubated for about 10 minutes or until the optimal blue color density developed. Fifty µl of Stop Solution (a 0.5 N hydrochlorid acid) was added to each well, and color changed from blue to yellow. The absorbance was red on a microplate reader at a wavelength of 450 nm immediately. The mean value of the triplicate readings for each standard and sample was calculated. To generate a Standard Curve, the graph was plotted on a special log/log paper using the standard concentrations on the x-axis and the corresponding mean 450 nm absorbance on the y-axis. The data may be linearized by using log/log paper and regression analysis may be applied to the log transformation. The unknown sample concentration was determined from the Standard Curve and multiplied by the dilution factor (2). The Standard Curve was run for each plate. The minimum detectable dose of TF is 10 pg/ml, typically.

3.2.2. Interleukin 6 ELISA assay

Plasma IL-6 was measured by ELISA using commercially available reagent (R&D Systems, Abingdon, Oxon, UK). All reagents were brought to room temperature before use. 96-well polystyrene microplates (12 strips of 8 wells)

were coated with 100 µL per well of the Primary (Capture) Antibody (360 µg/mL of mouse anti-human IL-6 R diluted to a working concentration of 2.0 µg/mL in phosphate-buffered saline (PBS): 112 µL of Capture Antibody diluted in 20 mL of PBS). PBS – 137 mM NaCl, 2.7 mM KCl, 8.1 mM Na2HPO4, 1.5 mM KH2PO4, pH 7.2-7.4, 0.2 µm filtered. The plates were sealed and incubated overnight in the fridge. The microplates were washed three times with 400 µL Wash Buffer (0.05 % Tween® in PBS, pH 7.2 – 7.4) next day. After the last wash, microplates were inverted, hit five times on absorbent paper towel to complete Wash Buffer removing. Then plates were blocked with 100 µL per each well of the mixture of milk powder (2.5 g of milk powder in 50 mL of Wash Buffer) and incubated at room temperature for a minimum of 1 hour. Plates were washed three times as above. 100 µl of standard or plasma was added per well, then wells were incubated for two hours. Standard preparation and dilution: the standard (recombinant human IL-6) was diluted to a working concentration of 4.0 ng/mL in Wash Buffer. 200 µL of standard solution was added into top wells of the 11th and 12th columns of the microplates and 150 µL of Wash Buffer into the next seven wells of the both columns. Then 1:4 dilutions were made using pipettes until the 7th wells of both strips. The 8th wells were left blank. Standard solutions were mixed well with multichannel pipette and put out 50 µL from each well. The microplates were left at room temperature for 2 hours. Plates were washed three times as above. After the washing, microplates were coated with 100 µL per well of the Secondary (Detection) Antibody (360 µg/mL of human IL-6 biotinylated antibody diluted to a working concentration of 2.0 µg/mL in Wash Buffer: 112 µL of the Secondary Antibody diluted in 20 mL of Wash Buffer) and incubated at room temperature for 1.5 – 2.0 hours. Plates were washed three times as above and 100 µL of streptavidin/HRP (streptavidin conjugated to horseradish-peroxidase) diluted 1:200 in Wash Buffer was added to each well. The plates were covered and left at room temperature for at least 30 minutes. Plates were washed again three times as above and 100 µL of substrate (1:1 mixture of Color Reagent A

(H2O2) and Color Reagent B (tetramethylbenzidine)). The substrate mixture has been done after the washing of microplates to avoid a change of color. After the incubation of 30 minutes, 50 μL of Stop Solution (2 N NH2SO4) was added to each well. The determination of the optical density of each well, the drawing of Standard Curve and calculation of plasma IL-6 concentrations were performed as is described above. A lower limit of detection was 0.7 pg/L.

3.2.3. Matrix metalloproteinase 9 ELISA assay

Plasma MMP-9 was measured by ELISA using commercially available reagent (R&D Systems, Abingdon, Oxon, UK). All reagents were brought to room temperature before use. 96-well polystyrene microplates (12 strips of 8 wells) were coated with 100 μL per well of the Primary (Capture) Antibody (112 μL of a mouse anti-human MMP-9 solution diluted in 20 mL of a Coating Buffer). The Coating Buffer is a universal buffer using to stabilize coated proteins by maintaining their tertiary three-dimensional structure, allowing for greater binding reactivity with the detection molecule, thereby enhancing the specific signal. The microplates were sealed and incubated overnight in the fridge. Plates were washed three times with 400 μL Wash Buffer next day. After the last wash, microplates were inverted, hit five times on absorbent paper towel to complete Wash Buffer removing. Then plates were blocked with 100 μL per each well of the mixture of milk powder (2.5 g of milk powder in 50 mL of Wash Buffer) and incubated at room temperature for a minimum of 1 hour. Plates were washed three times as above. One hundred μl of standard or 1:100 plasma (10 μL of plasma in 990 μL of Wash Buffer) was added per well, then wells were incubated for two hours. Standard preparation and dilution: the standard (recombinant human MMP-9) was diluted to a working concentration of 6.0 ng/mL in Wash Buffer. 200 μL of standard solution was added into top wells of the 11th and 12th columns of the microplates and 100 μL of Wash Buffer into the next seven wells of the both strips. Then 1:2 dilutions were made using pipettes until the 7th wells

of both strips. The last wells were left blank. Standard solutions were mixed well with multichannel pipette. Microplates were left at room temperature for at least 2 hours. Plates were washed three times as above. After the washing, microplates were coated with 100 μL per well of the Secondary (Detection) Antibody (112 μL of a human MMP-9 biotinylated antibody diluted in 20 mL of Wash Buffer) with multichannel pipette and incubated at room temperature for a minimum of 2 hours. Plates were washed three times as above and 100 μL of streptavidin diluted 1:200 in Wash Buffer was added to each well. Plates were covered and left at room temperature for at least 30 minutes. Plates were washed again four times as above and 100 μL of substrate (1:1 mixture of Color Reagent A and Color Reagent B). After the incubation of 30 minutes, the reaction was stopped by adding of 50 μL of Stop Solution (2 N NH2SO4) to each well. The determination of the optical density of each well, the drawing of Standard Curve and calculation of plasma MMP-9 concentrations were performed as is described above.

3.2.4. Tissue inhibitor of matrix metalloproteinase 1 ELISA assay

Plasma TIMP-1 was measured by ELISA using commercially available reagent (R&D Systems, Abingdon, Oxon, UK). The assay was performed exactly as plasma MMP-9 assay described above.

3.2.5. Von Willebrand factor ELISA assay

Plasma vWF was measured by ELISA using commercially available reagent (Dako-Patts, Ely, UK). All reagents and plasma samples were brought to room temperature before use. 96-well polystyrene microplates (12 strips of 8 wells) were coated with 50 μL per well of the Primary (Capture) Antibody diluted in a Coating Buffer. The microplates were sealed and incubated at least for 3 hours in the fridge. Plates were washed three times with 200 μL Wash Buffer. After the last wash, microplates were inverted, hit five times on absorbent paper

towel to complete Wash Buffer removing. Fifty µl of standard or 1:40 plasma diluted Wash Buffer was added per well, then wells were incubated for a minimum of two hours. Standard was prepared in 4 different concentrations, detected during chromatography as 'high', 'orange', 'medium', and 'low'. Plates were washed three times as above. Fifty µl of the Secondary Antibody (biotinylated polyclonal antibody against vWF) was added to each well; plates were incubated for two hours and then washed trhee times with 200 µl of Wash Buffer as above. Fifty µl of Chromogen Substrate (stabilized peroxidase chromogen substrate tetramethylbenzidine) per well was added and incubated for about 10 minutes or till the optimal blue color density developed. Fifty µl of Stop Solution (a 0.5 N hydrochlorid acid) was added to each well, and color changed from blue to yellow. The absorbance was red on a microplate reader at a wavelength of 492 nm immediately. The determination of the optical density of each well, the drawing of Standard Curve and calculation of plasma vWF concentrations were performed as is described above. A lower limit of detection was 0.5 IU/dL.

3.2.6. High sensitivity C-reactive protein assay

Plasma hs-CRP was measured with ultra sensitive reagents from Biokit, S.A. by assay using auto analyzer IL600 (Instrument Laboratories). It was a latex agglutination automated test for the quantitative determination of low levels of plasma CRP by turbodimetry. The assay was performed at the Sandwell Hospital, Birmingham, UK The lower limit of CRP sensitivity was 0.01mg/L, and inter-assay and intra-assay coefficient of variation were 8 % and 5 %, respectively.

3.3. Tissue samples collection and immunohistochemistry

The LAA and the RAA were harvested with minimal trauma, and processed as described below. The RAA tissue samples were obtained during cannulation

of the RAA just before the CPB, and the LAA tissue samples were excised immediately after the cardioplegia. The LAA and RAA of each patient were carefully lifted up with fingers, delivered to the surface, and gently held by forceps at the base. The appendages were cleanly amputadet distal to their base using a surgical scalpel, thereby avoiding any damage to the specimen. Tissues obtained from the LAA and RAA were immediately fixed in buffered 10% formalin, processed overnight, and embedded in paraffin wax within 48 hours. The embedding process was performed at the Institute of Cardiology, Lithuanian University of Health Science, Kaunas, Lithuania. Immunohistochemistry and its assessment were performed in the Haemostasis, Thrombosis and Vascular Biology Unit, City Hospital, Birmingham, United Kingdom. Serial sections were cut at a thickness of 3 μm on charged slides, and were deparaffinised and rehydrated prior to staining. The antibodies were tested at different dilutions on control tissue. Appropriate control tissue (as recommended by the manufacturer's data sheet) was used to test antibody staining. The control tissue and dilution that gave the desired staining without any background staining were selected. Positive and negative (omission of primary antibody) controls were included in every run. Antigen retrieval was carried out with two methods. Heat-induced antigen retrieval was performed with microwave oven. Sections were placed in a pressure cooker containing Tris/EDTA buffer (pH 7.8). The pressure cooker was placed in a microwave and heated for different time intervals, according to the antibody. Enzyme antigen retrieval was performed with Protease I (Ventana Medical Systems, Tucson, AZ, USA). Table 9 shows the antibodies used and the different retrieval methods.

All immunohistochemical staining was performed on a Ventana NexES automated stainer with a standard streptavidin-biotin-peroxidase technique (iVIEW DAB detection Kits; Ventana Medical Systems, Tucson, AZ, USA), as follows. The primary antibody was applied, and then located with biotin-conjugated secondary antibody. This step was followed by the addition of

a streptavidin enzyme (streptavidin-horseradish peroxidise; R&D systems, Abingdon, Oxon, UK) conjugate that binds to the biotin present on the secondary antibody. The complex was then visualized with hydrogen peroxide substrate and 3'3-diaminobenzidine tetrahydrochloride (DAB) chromogen. Ventana iVIEW DAB detection kits were used for all staining. The kits incorporate an inhibitor that blocks any endogenous peroxidase activity in the tissue. Note, that this level of staining cannot differentiate vWF in Weibel – Palade bodies or at the cell surface. After staining, sections were lightly counterstained with hematoxyllin, dehydrated, cleared, and coverslipped. Tissue sections were cut and stained together in a single batch by a single technician.

Slides were photographed together in a single run with the same illumination and exposure time, and on the same microscope (Olympus BX51 microscope fitted with an Olympus Colour View Camera [Olympus Soft Imaging Solutions, Gmbh, Southend-on-Sea, UK] and Olympus Cell B software). The light intensity was kept constant with the 'Pre-set' button of the microscope at the start of the session.

Tissues were examined independently by two board-certified consultant histopathologists (U.Z. and M.M.), who both scored each slide as having no staining, weak focal staining, multifocal moderate staining, or diffuse strong staining, giving a score of 0, 1, 2, or 3, respectively. IL-6, MMP-9 and TINP-1 were assessed on endocardium, epicardium, and cardiomyocytes. vWF and tissue factor were assessed on endocardium. Staining and scoring were performed with the two independent investigators blinded to the AF status of the patients. The means of individual staining scores were used for analysis, and then adjusted by a third party so that pooled mean scores of 0, 0.5 and 1 were recorded as 1 (low-intensity staining), pooled mean scores of 1.5 and 2.0 were rescored as 2 (moderate-intensity staining), and pooled mean scores of 2.5 and 3.0 were rescored as 3 (high-intensity staining). The kappa statistic for agreement in staining between the observers was 0.58.

Table 9. Antibodies and retrieval techniques

Antibody	Manufacturer	Antigen retrieval	Dilution	Incubation (min)	Control tissue
Matrix metalloproteinase-9	Novocastra, Newcastle Upon Tyne, UK	Tris/EDTA buffer, 15 min	1 : 10	32	Kidney/liver
Interleukin-6	Dako, Glostrup, Denmark	None	1 : 40	32	Appendix
Tissue factor	American Diagnostica, Stamford, CT, USA	Protease 1, 10 min	1 : 200	32	Pancreas
Von Willebrand factor	Dako, Glostrup, Denmark	Tris/EDTA buffer, 15 min	1 : 1000	32	Tonsil
Tissue inhibitor of metalloproteinase-1	Dako, Glostrup, Denmark	Tris/EDTA buffer, 12 min	1 : 100	32	Pancreas

3.4. Electron microscopy

RAA and LAA tissue biopsies from twenty patients were blindly selected for electron microscopy. A small portion of each specimen was separated from the fresh tissue sample intended for immunohistochemistry analysis before fixation, cut into 1 mm3 pieces, fixed in Karnovsky's solution, placed onto an ice and transported to the Institute of Experimental and Clinical Medicine (Centre of Innovative Medicine), Vilnius University, Vilnius, Lithuania, where further preparations and analysis were done. Fixed tissue specimens were left at 4 °C overnight. Thereafter, the tissue samples were washed in phosphate buffer (3 x 15 min) and transferred into 1% osmium tetroxide solution for 1 hour at 4 °C. It was then rinsed again in the phosphate buffer. After washing the tissue pieces were dehydrated through a graded series of ethanol solutions and propylene oxide. Then tissue pieces were placed into BEEM capsules and cured in a 68 °C oven overnight. Thick sections were cut using a glass knife at a 45 degree angle 1 to 3 micron thick from the embedded blocks and placed onto glass slides. Thin (70 nm) sections were cut from the sick section slides using the LKB III Ultramicrotome and placed onto clean 200-mesh copper grids. The grids were stained with uranyl acetate and lead citrate, rinsed and placed

into grid holders. The grids were viewed in the JEM-100B transmission electron microscopy at an accelerating voltage of 60 kV and photomicrographs were made. These photomicrographs were examined together with the pathologist (V.G.).

3.5. Statistical analysis

A hypothesis has been brought up that a difference of one half of SD in our test statistic of hs-CRP between those patients with or without post-operative AF, where data from 34 subjects in each of two groups for alpha $2p < 0.05$ and 1-beta = 0.8 were sufficient. Therefore predicting an AF rate of approximately 30% (1 – 4) we aimed to recruit at least 100 subjects.

Following a test of statistical normality, analyses using parametric and non-parametric tests were performed as appropriate, vWF was normally distributed and expressed as mean (standard deviation, SD), whilst IL-6, TF, MMP-9, TIMP-1, hs-CRP were non-parametrically distributed and expressed as median (interquartile range, IQR). Differences between patient subgroups (AF vs. non-AF) were determined by t-test for normally distributed variables and by Mann Whitney U-test equivalent for non-normally distributed variables. The Chi2 – test was used for categorical variables, i.e. the expression of markers. Spearman rank correlation method was used to determine statistical correlation between measured biomarkers and age, blood pressure etc. Differences in biomarkers between various sampling sites were determined using by one-factor within-subjects ANOVA Bonferoni method for parametric variables and Friedman test for non-parametric variables. If any significant difference was detected by Friedman test, variables between different sampling sites were compared by one-factor within-subjects ANOVA Bonferoni method after log-transformation of variables. The relationship between plasma vWF and the tissue expression of vWF was assessed as a continuum by Altman's linear ordered trend method [399]. $P < 0.05$ was considered as statistically significant. Power calculation was performed on Minitab 14 (Minitab, State College, Pennsylvania, USA). Statistical analyses were performed using SPSS, 14.0 for Windows (SPSS Inc., Chicago, Il, USA) and Minitab 14 (Minitab, State College, Pennsylvania, USA).

4. RESULTS

4.1. Patients clinical characteristic

Four patients did not finished the study and did not included into further analysis: one patient died during early postoperative period due to severe bleeding and multsystemic failure, three patients fell out from the study due to inability to collect blood and tissue samples from the LAA. One hundred consecutive patients (mean age 64, standard deviation 9 years) without prior history of AF within six months before the surgical intervention were followed-up for the development of postoperative AF, which was documented in 30 days. This enabled a case-control comparison of those at 30 days with AF (n = 30) compared to those who proceeded to 30 days in SR (n = 70). This outcome is comparable to published data on the development of postoperative AF [3 – 6] and justified our recruitment strategy. Patient clinical characteristics are presented in Table 10. Patients who developed AF were slightly older than those free of AF (63.2 ± 9.0 years vs. 67.0 ± 8.3 years, p = 0.047), other clinical variables did not differ between groups significantly.

Overall, plasma TF was lower in patients with hypertension or on antihypertensive therapy (median (IQR) 14 (10 – 19) pg/ml vs. 17.5 (14 – 26) pg/ml, p = 0.046) and IL-6 was higher in smokers compared to non-smokers (median (IQR) 24 (9.3 – 96.3) pg/ml vs. 7.8 (3.8 – 58.0) pg/ml, p = 0.028).

Table 10. Patient characteristics

	Postoperative AF		
	No (n=70)	**Yes (n=30)**	**P value**
Gender: Male, n (%) Female, n (%)	 58 (82.9) 12 (17.1)	 28 (93.3) 2 (6.7)	 0.166
Age, years ± SD	63.2 ± 9.0	67.0 ± 8.3	**0.047**
History of MI, n (%)	29 (41.4)	15 (50)	0.429

	Postoperative AF		
	No (n=70)	Yes (n=30)	P value
Arterial hypertension, n (%)	59 (84.3)	25 (83.3)	0.905
Diabetes mellitus or impaired glucose tolerance, n (%)	13 (18.6)	5 (16.7)	0.820
Current smoking, n (%)	20 (28.6)	11 (36.7)	0.422
Echocardiographic data [mm ± SD]			
Interventricular septum,	12.4 ± 1.8	12.7 ± 1.4	0.347
LV end-diastolic diameter	52.8 ± 5.0	55.0 ± 5.2	0.052
LA diameter	52.7 ± 4.6	53.7 ± 5.7	0.319
RA diameter	48.2 ± 4.4	49.3 ± 6.1	0.303
LV ejection fraction, % ± SD	52.2 ± 7.2	50.0 ± 7.7	0.189
Creatinine, μmol/L ± SD	93.8 ± 22.3	100.0 ± 21.2	0.238
Haemoglobin, g/L ± SD	144.0 ± 13.0	140.2 ± 14.9	0.201
Leucocytes, $x10^9$/L ± SD	6.8 ± 1.6	7.3 ± 1.6	0.106
Platelets, $x10^9$/L ± SD	236.2 ± 58.8	236.7 ± 57.8	0.973
CPB time, min. ± SD	111.1 ± 22.4	118.4 ± 21.6	0.136
Aortic cross-clamp time, min. ± SD	72.3 ± 20.0	80.8 ± 20.8	0.057
Number of grafts, number ± SD	4.2 ± 0.8	4.4 ± 0.9	0.204
Haemodynamic instability, n (%)	15 (21.4)	9 (30)	0.358
Use of statins preoperatively, n (%)	10 (14.3)	4 (13.3)	0.900

AF – atrial fibrillation, CPB – cardiopulmonary bypass, LA – left atrial, LV – left ventricular, MI – myocardial infarction, RA – right atrial, SD – standard deviation, SR – sinus rhythm.
$P < 0.05$ considered as significant.

4.2. Results of plasma analysis

Hs-CRP levels were higher in AF patients in peripheral blood (PB) and in blood taken from the RAA and LA compared to patients in SR (Table 11). Across the whole cohort, hs-CRP levels were significantly different between sampling sites, with the lowest levels of hs-CRP in the LAA (posthoc test, $p < 0.001$) (Figure 1). Differences in hs-CRP levels were evident between different sampling sites in the postoperative AF and SR groups, with the lowest levels in the LAA (posthoc test, $p < 0.001$) (Figure 2). IL-6 levels were also higher in the AF than the SR group in samples obtained from the RAA ($p = 0.031$), LA ($p = 0.042$) and LAA ($p = 0.006$).

IL-6 levels were not significantly different between the five sampling sites in the whole cohort, in the patients with postoperative AF, or in the patients in SR group. There were no differences in levels of plasma TIMP-1 in the samples from the AF versus the SR group patients in any of the five sampling sites (Table 12). However, in the whole cohort, there were significant inter-site differences in plasma TIMP-1 levels. The lowest TIMP-1 levels were found in the LAA (posthoc test, LAA vs. RA and LAA vs. RAA, both $p < 0.001$), and in the LA compared to the RAA ($p = 0.02$). In the SR group, TIMP-1 was lower in the LAA blood compared to the PB sample, the RA blood and the RAA blood ($p < 0.01$). Significant differences in plasma TIMP-1 levels were found only between the LAA and the RAA bloods in patients who developed postoperative AF, with lower levels in the LAA ($p = 0.039$). Levels of MMP-9 were higher in the AF patients compared to the SR group patients only in the LAA blood samples. In the whole cohort, there were significant inter-site differences in plasma MMP-9. Those who remained in SR had significantly lower plasma MMP-9 levels in the LA blood versus the PB ($p = 0.038$). The TIMP-1/MMP-9 ratio was significantly different between the sampling sites ($p < 0.001$) in the whole cohort, with the lowest ratio in the LAA versus RA, RAA and LA ($p = 0.007$, $p = 0.012$, $p = 0.011$, respectively), and in the PB versus RA ($p = 0.009$). The lower TIMP-1/MMP-9 ratio in the LAA versus the RAA and the RA ($p = 0.013$ and $p = 0.035$, respectively) was determined in patients who developed AF after CABG, but no significant inter-site differences were found in SR group.

Amongst patients who developed postoperative AF, MMP-9 levels were significantly higher in the LAA, when compared to those from the LAA in SR group ($p = 0.007$). Plasma levels of TIMP-1 and ratio TIMP-1/ to MMP-9 did not significantly differ between patients who developed postoperative AF and those remained in SR (Table 12).

Plasma vWF levels in patients who developed AF were not significantly different from those who remained in SR irrespective of sampling site (Table 13). In

the whole cohort, vWF levels in blood from the LAA were significantly lower compared to other sampling sites (posthoc test, $p < 0.001$ for LAA blood vs. PB, LAA vs. RA blood, LAA vs. RAA blood, and $p = 0.004$ for LAA vs. LA blood). In the AF subgroup lower vWF levels were found in the LAA blood vs. PB ($p = 0.011$). There were no significant differences in plasma TF in those who had postoperative AF compared to those who remained free of AF. Overall, significantly higher plasma TF levels were found in the LAA blood compared to the PB ($p = 0.001$) and the LA blood ($p = 0.016$), as well as in the RA blood compared to the PB ($p = 0.007$). In the AF patients, higher plasma TF levels were found in the LAA blood compared to those in the PB, RAA blood and LA blood ($p = 0.011$, $p = 0.034$, and $p = 0.014$, respectively).

In multiple stepwise regression analysis, after adjusting for age, gender, smoking, diabetes, previous history of AF, postoperative AF, previous history of myocardial infarction, presence of arterial hypertension, systolic and diastolic blood pressure, we did not find any predictors for vWF ($p = NS$).

Levels of plasma hs-CRP from the PB, the RAA and the LA were positively associated with development of postoperative AF ($p = 0.023$, $p = 0.025$ and $p = 0.031$, respectively). Plasma IL-6 levels in the RA and in the LA were positively associated with occurrence of postoperative AF ($p = 0.048$ and $p = 0.012$, respectively).

Plasma TIMP-1 levels obtained from the PB were associated positively with age ($p = 0.001$). TIMP-1 levels in the RA and in the RAA were positively associated with age ($p = 0.007$ and $p = 0.003$, respectively). Plasma MMP-9 levels in the LAA were positively associated with the development of postoperative AF ($p = 0.009$).

Table 11. Inflammatory indices (hs-CRP and IL-6) levels, by sampling site and effects of postoperative atrial fibrillation.

	Sampling site	PV	RA	RAA	LA	LAA	P value
(a) hs-CRP mg/L (IQR)	Whole cohort	1.9 (1.1-6.4)	1.7 (1.0-5.9)	2.0 (1.0-6.7)	1.8 (0.9-5.9)	1.4 (0.7-4.2)	<0.001
	Postoperative AF						
	No	1.6 (1.0-4.4)	1.5 (1.0-4.0)	1.5 (1.0-3.9)	1.4 (0.9-4.2)	1.0 (0.7-4.3)	<0.001
	Yes	3.7 (2.1-8.4)	2.9 (1.3-8.3)	3.6 (1.8-8.7)	3.2 (1.4-7.1)	2.4 (0.7-6.6)	<0.001
p value, postoperative AF vs. SR		0.018	0.074	0.029	0.026	0.123	
(b) IL-6, pg/ml (IQR)	Whole cohort	16.0 (4.0-65.0)	15.8 (4.5-61.3)	13.5 (4.0-66.3)	17.0 (4.0-62.5)	17.0 (4.4-54.3)	0.284
	Postoperative AF						
	No	9.8 (4.0-60.0)	13.0 (4.2-49.5)	10.5 (3.4-52.5)	13.5 (3.0-58.5)	13.0 (3.6-27.8)	0.334
	Yes	32.0 (6.4-88.8)	40.0 (7.0-86.3)	47.0 (7.4-90.0)	35.0 (8.3-85.0)	38.0 (14.5-67.8)	0.177
p value, postoperative AF vs. SR		0.075	0.076	0.031	0.042	0.006	

AF – atrial fibrillation, SR – sinus rhythm, hs-CRP – high sensitive C-reactive protein, IL-6 – interleukin-6, PV – peripheral vein, RA – right atrium, RAA – right atrial appendage, LA – left atrium, LAA – left atrial appendage. $P < 0.05$ considered as significant.

Table 12. Extracellular matrix turnover indices (MMP-9, TIMP-1 and their ratio) levels, by sampling site and effects of postoperative atrial fibrillation.

	Sampling site	PV	RA	RAA	LA	LAA	P value
(a) TIMP-1, pg/ml (IQR)	Whole cohort	960 (720-1150)	980 (760-1200)	980 (755-1250)	930 (715-1100)	860 (635-1050)	<0.001
	Postoperative AF						
	No	940 (740-1150)	980 (757-1150)	930 (735-1212)	920 (650-1112)	830 (595-1000)	<0.001
	Yes	1000 (700-1200)	990 (800-1337)	1100 (885-1287)	950 (790-1125)	930 (720-1125)	0.018
p value, postoperative AF vs. SR		0.686	0.418	0.073	0.337	0.088	
(b) MMP-9, pg/ml (IQR)	Whole cohort	745 (492-985)	700 (487-865)	710 (500-965)	600 (455-905)	650 (470-1062)	0.03
	Postoperative AF						
	No	700 (470-985)	710 (500-825)	720 (500-985)	590 (424-863)	600 (457-910)	<0.001
	Yes	790 (580-1062)	680 (447-1050)	650 (485-960)	690 (460-1400)	810 (610-1812)	0.622
p value, postoperative AF vs. SR		0.526	0.885	0.746	0.159	0.007	
(c) TIMP-1: MMP-9 ratio median (IQR)	Whole cohort	1.2 (0.8-2.0)	1.5 (1.0-2.1)	1.4 (1.0-2.0)	1.4 (1.0-2.1)	1.2 (0.8-1.8)	<0.001
	Postoperative AF						
	No	1.3 (0.8-2.0)	1.5 (1.0-2.0)	1.3 (1.0-1.8)	1.4 (1.1-2.1)	1.2 (0.8-2.0)	0.009
	Yes	1.2 (0.9-1.9)	1.6 (1.1-2.4)	1.7 (1.0-2.2)	1.5 (0.7-2.2)	1.0 (0.6-1.6)	0.032
p value, postoperative AF vs. SR		0.727	0.531	0.112	0.729	0.132	

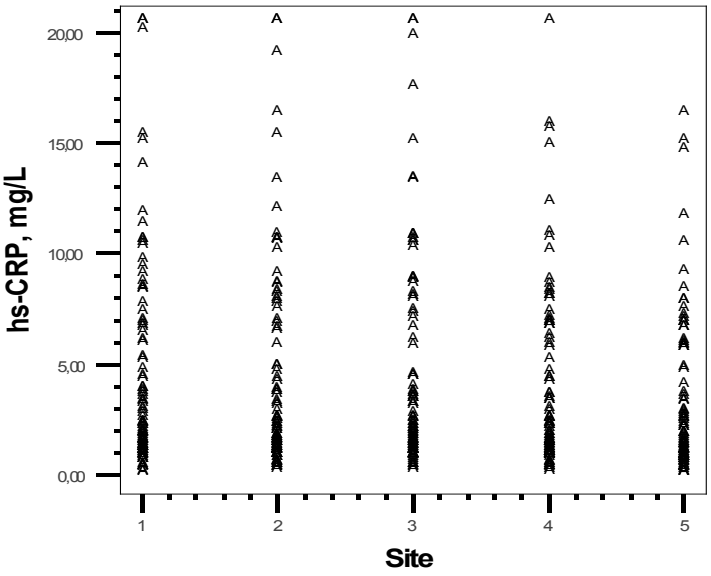
AF – atrial fibrillation, SR – sinus rhythm, MMP-9 – matrix metalloproteinase-9, TIMP-1 – tissue inhibitor of matrix metalloproteinase-1, PV – peripheral vein, RA – right atrium, RAA – right atrial appendage, LA – left atrium, LAA – left atrial appendage. $P < 0.05$ considered as significant.

Table 13. von Willebrand factor and Tissue Factor levels, by sampling site and effects of postoperative atrial fibrillation.

	Sampling site	PV	RA	RAA	LA	LAA	P value
(a) vWF, IU/dL, mean ±SD	Whole cohort	127.2 ±26.5	124.8 ±23.4	126.7 ±26.8	121.3 ±25.4	112.4 ±27.7	<0.001
	Postoperative AF						
	No	125.8 ±26.9	124.6 ±24.5	125.8 ±27.6	119.3 ±26.0	110.3 ±28.4	<0.001
	Yes	131.1 ±26.3	125.7 ±20.7	128.3 ±24.5	126.0 ±23.4	120.2 ±23.0	0.007
p value, postoperative AF vs. SR		0.369	0.825	0.673	0.223	0.096	
(b) Tissue Factor pg/ml (IQR)	Whole cohort	14.0 (10.8-19.0)	16.0 (13.0-21.3)	15.0 (12.0-23.0)	15.0 (11.0-21.0)	17.5 (12.5-26.3)	<0.001
	Postoperative AF						
	No	14.0 (10.8-19.0)	16.5 (13.8-22.3)	15.5 (12.0-13.3)	15.0 (11.8-21.0)	17.0 (12.5-26.0)	0.026
	Yes	14.0 (9.8-18.5)	14.0 (11.0-20.0)	14.0 (11.0-23.0)	16.5 (10.0-22.3)	19.0 (13.0-27.0)	0.002
p value, postoperative AF vs. SR		0.501	0.201	0.489	0.969	0.316	

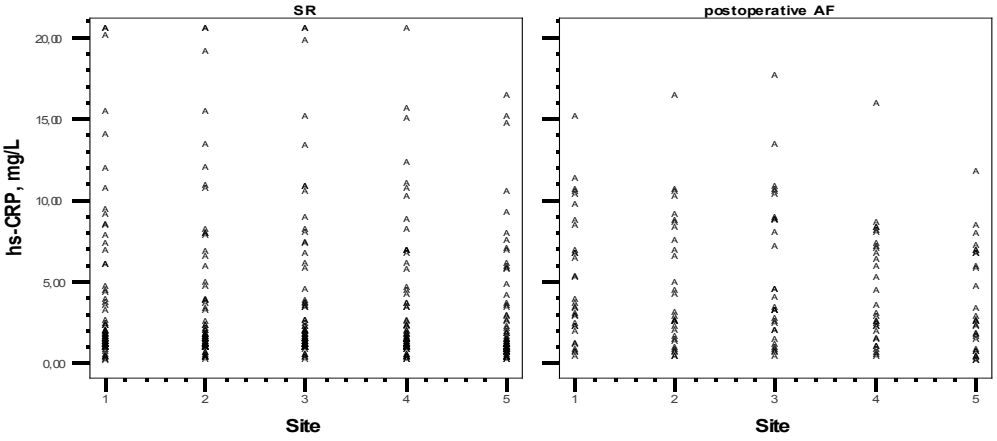
AF – atrial fibrillation, SR – sinus rhythm, vWf – von Willebrand factor, PV – peripheral vein, RA – right atrium, RAA – right atrial appendage, LA – left atrium, LAA – left atrial appendage. $P < 0.05$ considered as significant.

Figure 1. hs-CRP levels between different sampling sites in the whole cohort



1 - peripheral/femoral vein; 2 - right atrium;
3 - right atrial appendage; 4 - left atrium;
5 - left atrial appendage

Figure 2. hs-CRP levels between different sampling sites in sinus rhythm (SR) and postoperative atrial fibrillation (AF) groups



1 - peripheral/femoral vein; 2 - right atrium;
3 - right atrial appendage; 4 - left atrium;
5 - left atrial appendage

4.3. Immunohistochemistry data

A cardiac expression of vWF, TF, MMP-9, TIMP-1 and IL-6 in the group as whole is shown in Table 14. There was no difference in the expression of the markers between LAA and RAA tissues. Expression levels of the markers by the endocardium of the RAA and the LAA were as follows: vWF > TF > IL-6 > MMP-9 = TIMP-1 (both $p < 0.001$). Expression of the tissue remodeling markers by endocardium was minimal. However, IL-6, MMP-9 and TIMP-1 staining was significantly higher in both LAA and RAA epicardial tissue than in the endocardial tissue ($p < 0.001$). Notably, MMP-9 expression by cardiomyocytes was equivalent to that by epicardial tissue.

Table 15 shows data according to the presence of AF within 30 days of CABG. More intense expression of vWF by LAA tissue was the only predictor of those patients who went on to have AF as compared with those who were free of AF. Expression of vWF in SR group patients was low in 16.7 % of patients, moderate in 65.1 %, and high in 18.2 %, as compared with a profile of 24.2 % – 31.0 % – 44.8 %, respectively, in those who developed postoperative AF ($p = 0.006$). Figure 3A – C shows typical results of the staining of endocardial tissue for the intensity of vWF. In Figure 3A, the intensity of staining is low, scoring 1+. In Figure 3B, the intensity of staining is moderate, scoring 2+. Finally, in Figure 3C, the intensity of staining is high, scoring 3+. The strength of the staining clearly increases across these three figures. In contrast, the counterstaining is of equal intensity in each figure.

Expression of IL-6, MMP-9 and TIMP-1 by epicardial tissue, cardiomyocytes and endocardial tissue was approximately the same as in combined group, and all failed to predict AF.

The relationship between plasma vWF and the continuum of increasing tissue expression of vWF was assessed by Altman's linear ordered trend method [399], and is shown in Table 16. Mean plasma vWF increased by 13.5 % with greater LAA tissue expression ($p < 0.05$), but only when all subjects were pulled. Although a clear ordered trend of increasing vWF was present in the LAA tissue in the patients

from SR group (rising by 11.2 %), the LAA tissue in the subjects who went on to suffer postoperative AF (14.8 %), and the RAA tissue in the patients who developed AF after CABG (10.6 %), these trends were not statistically significant, probably because of small subject numbers in each group.

Table 14. Tissue expression of von Willebrand factor, tissue factor, matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 and interleukin-6 by left atrial appendage and right atrial appendage tissue in 100 patients undergoing coronary artery bypass grafting.

Biomarkers	Relative expression (%) by LAA tissue (low – moderate – high)	Relative expression (%) by RAA tissue (low – moderate – high)	LAA/RAA p-value
vWF on endocardium	18 – 52 – 27	22 – 51 – 26	0.815
TF on endocardium	64 – 31 – 1	58 – 38 – 3	0.375
IL-6 on:			
Endocardium	89 – 8 – 0	91 – 8 – 1	0.409
Cardiomyocytes	88 – 9 – 0	92 – 8 – 0	0.749
Epicardium	50 – 27 – 12	56 – 26 – 12	0.895
P-value between tissues	< 0.001	< 0.001	
MMP-9 on:			
Endocardium	100 – 0 – 0	98 – 1 – 0	–
Cardiomyocytes	55 – 35 – 6	66 – 30 – 2	0.186
Epicardium	53 – 26 – 9	55 – 32 – 2	0.078
P-value between tissues	< 0.001	< 0.001	
TIMP-1 on:			
Endocardium	100 – 0 – 0	100 – 0 – 0	–
Cardiomyocytes	96 – 1 – 0	100 – 0 – 0	–
Epicardium	62 – 23 – 5	55 – 31 – 4	0.424
P-value between tissues	< 0.001	< 0.001	

– statistical analysis unsound. Data are number of tissues staining with low, moderate or strong intensity. P-values by chi-squared test. Numbers may fail to sum to 100, owing to insufficient tissue being obtained. IL-6 – interleukin-6, LAA – left atrial appendage, MMP-9 – matrix metalloproteinase-9, RAA – right atrial appendage, TF – tissue factor, TIMP-1 – tissue inhibitor of metalloproteinase-1, vWF – von Willebrand factor. $P < 0.05$ considered as significant.

Table 15. Tissue expression of von Willebrand factor, tissue factor, matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 and interleukin-6 by left atrial appendage and right atrial appendage tissue according to the development of postoperative atrial fibrillation.

	Sinus rhythm group (n = 70)			**Postoperative AF group (n = 30)**				
	(1) LAA	**(2) RAA**	**P-value for LAA vs. RAA (1 vs. 2)**	**(3) LAA**	**(4) RAA**	**P-value for LAA vs. RAA (3 vs. 4)**	**P-value for LAA in SR group vs. LAA in AF group (1 vs. 3)**	**P-value for RAA in SR group vs. RAA in AF group (2 vs. 4)**
vWF	11–43–12	18–35–16	0.629	7 – 9 – 13	4 – 16 – 10	0.207	0.006	0.305
TF	44–22–1	41–27–2	0.113	20 – 9 – 0	17 – 11 – 1	0.514	0.826	0.410
IL-6 on:								
Endocardium	63–5–0	64–4–0	0.730	26 – 3 – 0	27 – 2 – 1	0.640	0.624	0.849
Cardiomyocytes	64–4–0	66–4–0	0.966	24 – 5 – 0	26 – 4 – 0	0.676	0.078	0.198
Epicardium	37–18–7	40–21–5	0.757	13 – 9 – 5	16 – 5 – 7	0.413	0.525	0.193
P-value of IL-6 expression between different layers	< 0.001	< 0.001		< 0.001	0.004			
MMP-9 on:								
Endocardium	68 – 0 – 0	70 – 0 – 0	–	29 – 0 – 0	28 – 1 – 0	–	–	–
Cardiomyocytes	36–28–4	47–21–1	0.119	20 – 6 – 3	19 – 10 – 1	0.366	0.142	0.567
Epicardium	36–21–5	38–22–2	0.502	18 – 5 – 4	18 – 9 – 1	0.232	0.273	0.678
P-value of MMP-9 expression between different layers	< 0.001	< 0.001		0.016	0.021			
TIMP-1 on:								
Endocardium	68 – 0 – 0	69 – 0 – 0	–	29 – 0 – 0	30 – 0 – 0	–	–	–
Cardiomyocytes	67 – 1 – 0	69 – 0 – 0	–	29 – 0 – 0	30 – 0 – 0	–	–	–
Epicardium	42–18–3	35–26–2	0.318	20 – 4 – 3	20 – 5 – 2	0.856	0.252	0.097
P-value of TIMP-1 expression between different layers	< 0.001	< 0.001		< 0.001	< 0.001			

– statistical analysis unsound. vWF and TF were stained on the endocardium only. Data are number of tissues staining with low, moderate or strong intensity. P-values by chi-squared test. Numbers may fail to sum to 70 or 30, owing to insufficient tissue being obtained. AF – atrial fibrillation, IL-6 – interleukin-6, LAA – left atrial appendage, MMP-9 – matrix metalloproteinase-9, RAA – right atrial appendage, SR – sinus rhythm, TF – tissue factor, TIMP-1 – tissue inhibitor of metalloproteinase-1, vWF – von Willebrand factor. $P < 0.05$ considered as significant.

Table 16. Relationship between plasma von Willebrand factor and the expression of von Willebrand factor by the endocardium of the left atrial appendage and the right atrial appendage.

	Staining intensity (1+)	Staining intensity (2+)	Staining intensity (3+)
LAA (all patients)	118 ± 18 (n = 18)*	125 ± 27 (n = 52)*	134 ± 27 (n = 27)*
RAA (all patients)	121 ± 27 (n = 22)	130 ± 26 (n = 51)	127 ± 25 (n = 26)
LAA (patients in SR)	116 ± 22 (n = 11)	124 ± 27 (n = 43)	129 ± 29 (n = 14)
RAA (patients in SR)	121 ± 11 (n = 18)	129 ± 25 (n = 35)	121 ± 21 (n = 16)
LAA (patients with postoperative AF)	121 ± 11 (n = 7)	126 ± 29 (n = 9)	139 ± 28 (n = 13)
RAA (patients with postoperative AF)	122 ± 14 (n = 4)	132 ± 26 (n = 16)	135 ± 30 (n = 10)

* $P < 0.05$ for linear trend. Data presented as mean level of plasma von Willebrand factor ± standard deviation. AF – atrial fibrillation, LAA – left atrial appendage, n – number of patients in each group, RAA – right atrial appendage, SR – sinus rhythm.

Figure 3A – C. Typical von Willebrand factor staining of a section of atrial appendage. A – low intensity, B – moderate intensity, C – high intensity. All figures are at a magnification x 40.

Figure 3A.

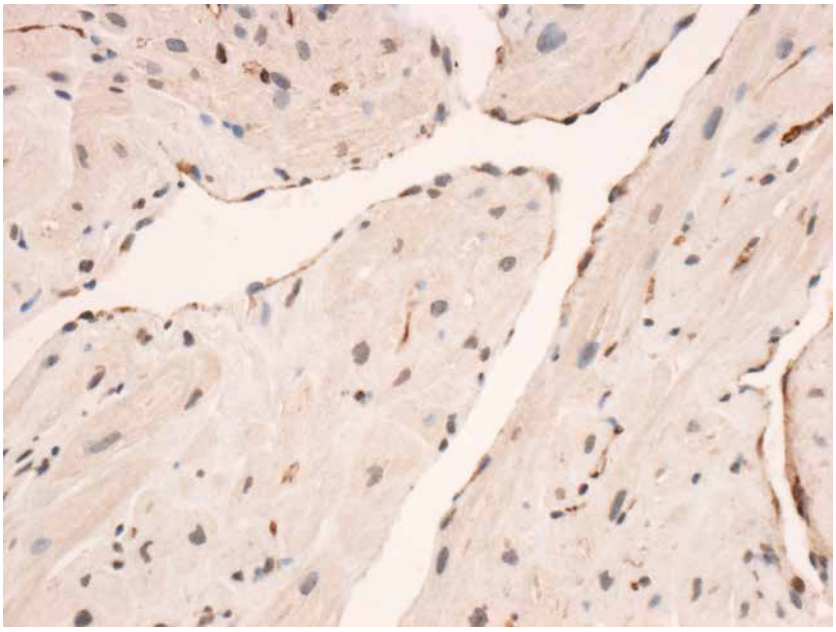


Figure 3B.

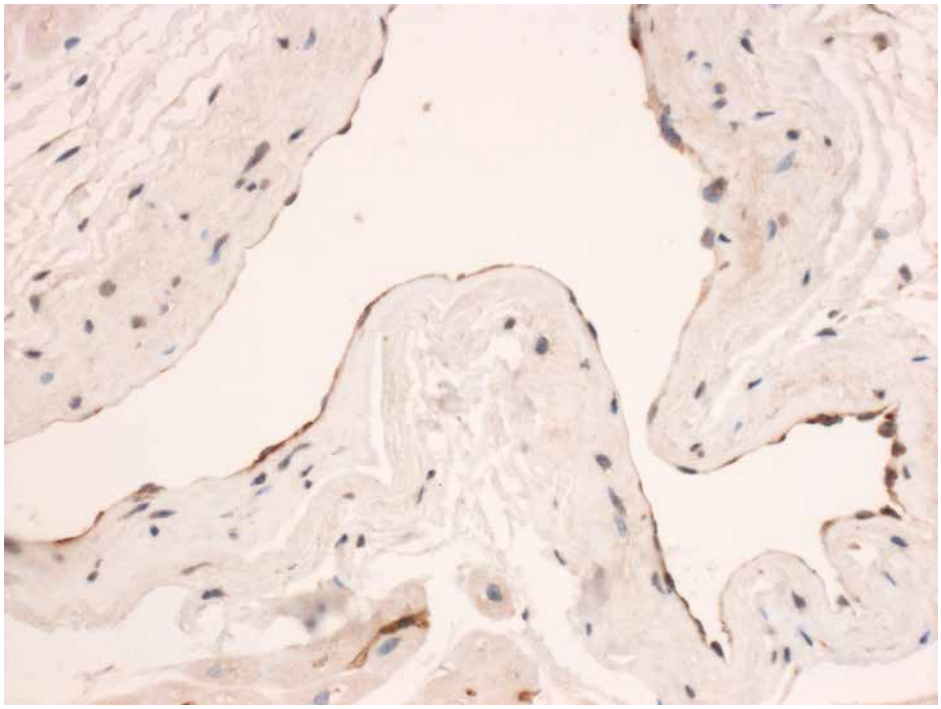
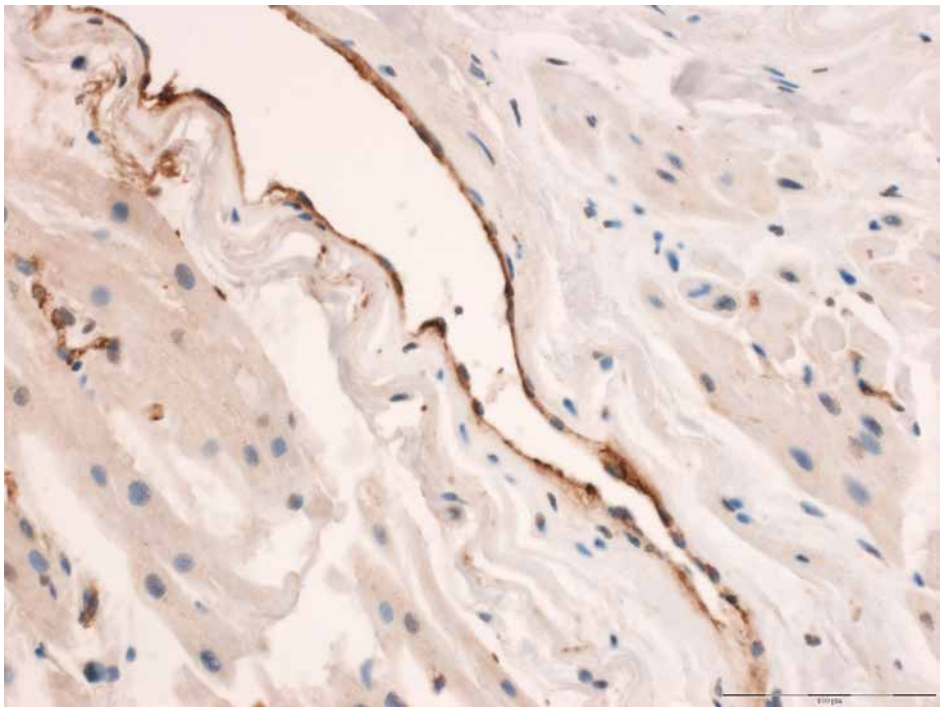


Figure 3C.



4.4. Electron microscopy findings

The electron microscopy evaluation is presented as descriptive and illustrative study, which did not reach a statistical reliability due to a small amount of cases had been assessed. The examination was performed on the LAA and RAA in 20 patients undergoing CABG (11 of them remained in sinus rhythm after the surgery and 9 had postoperative AF). The ultrastructural changes were found almost in all studied specimens of both atrial appendages regardless of the development of postoperative AF. The atrial ultrastructural changes and their scoring among both patients groups are presented in Table 17. The electron microscopy examination showed highly remodelled myocytes characterized by widespread lysis of sarcomers: the myofilaments were often thin and irregular with widened Z bands (Figure 4). The empty spaces in the myolytic areas were filled with sparse sarcomers, glycogen granules or detritus containing proteins (Figure 5). There were different and pronounced changes of mitochondria: elongated shape with inconstant longitudinal orientation of the cristae, lysis and condensation of cristae, rupture of mitochondrial wall (Figure 6A-E). Although an intercellular fibrosis of different degree was found almost in all tissue specimen (Figure 7A – D). An intercellular insertion of substrate from thin fibrils and protein was determined in many of cases (Figure 8). This substrate was completely different from collagen by its structure and reminded amyloid, but it was not proven by staining with Kongo red.

All pathological findings were qualitatively similar in both the LAA and RAA tissue samples (Table 18).

Figure 4. Pathologic sarcomers.

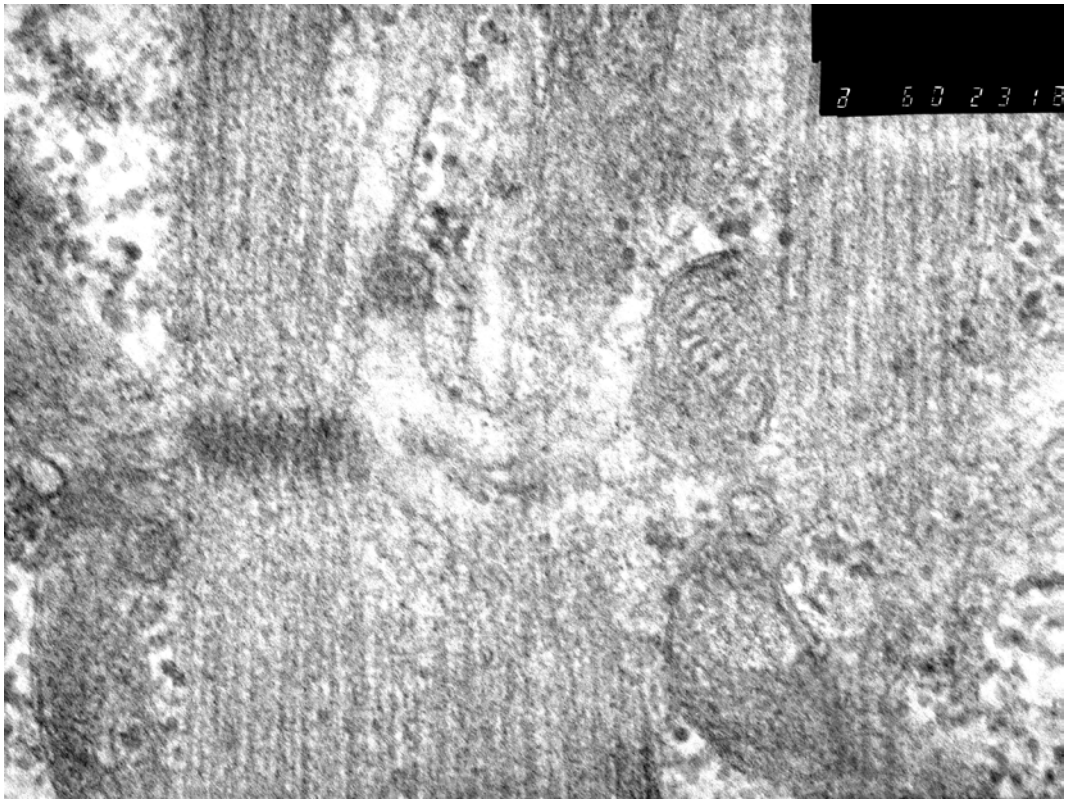


Figure 5. Complete destruction of sarcomer.

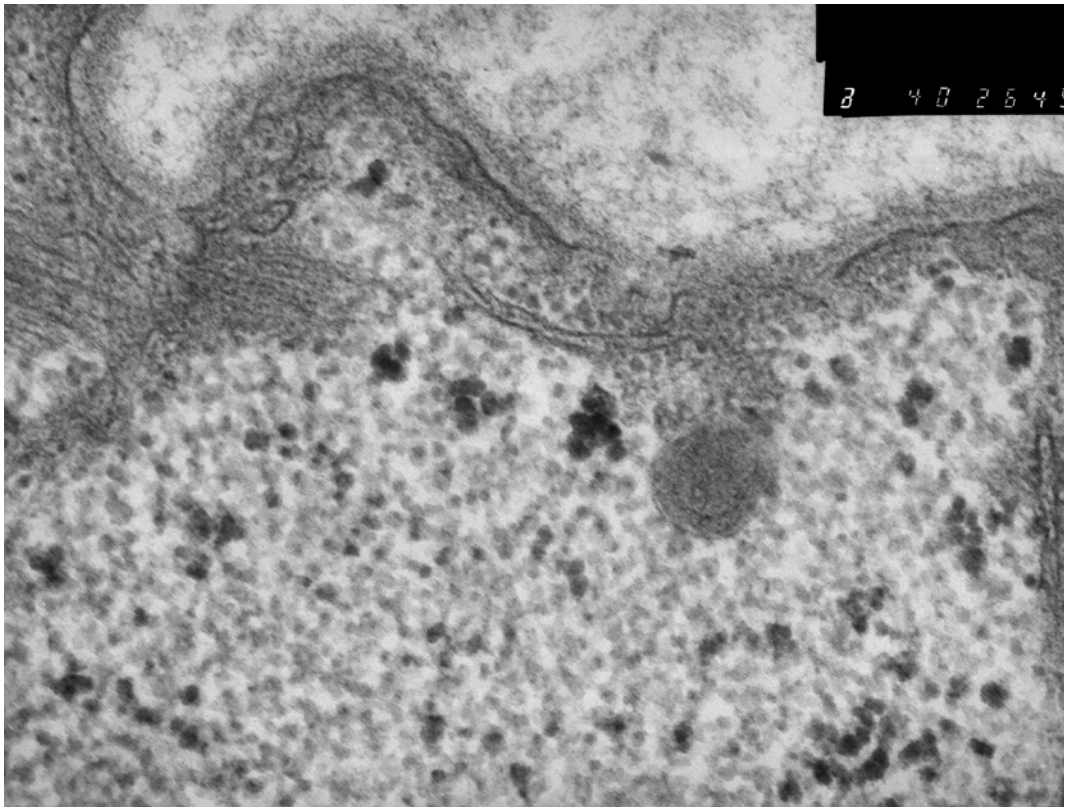


Figure 6A – E. Ultrastructural changes of mitochondria.

Figure 6A.

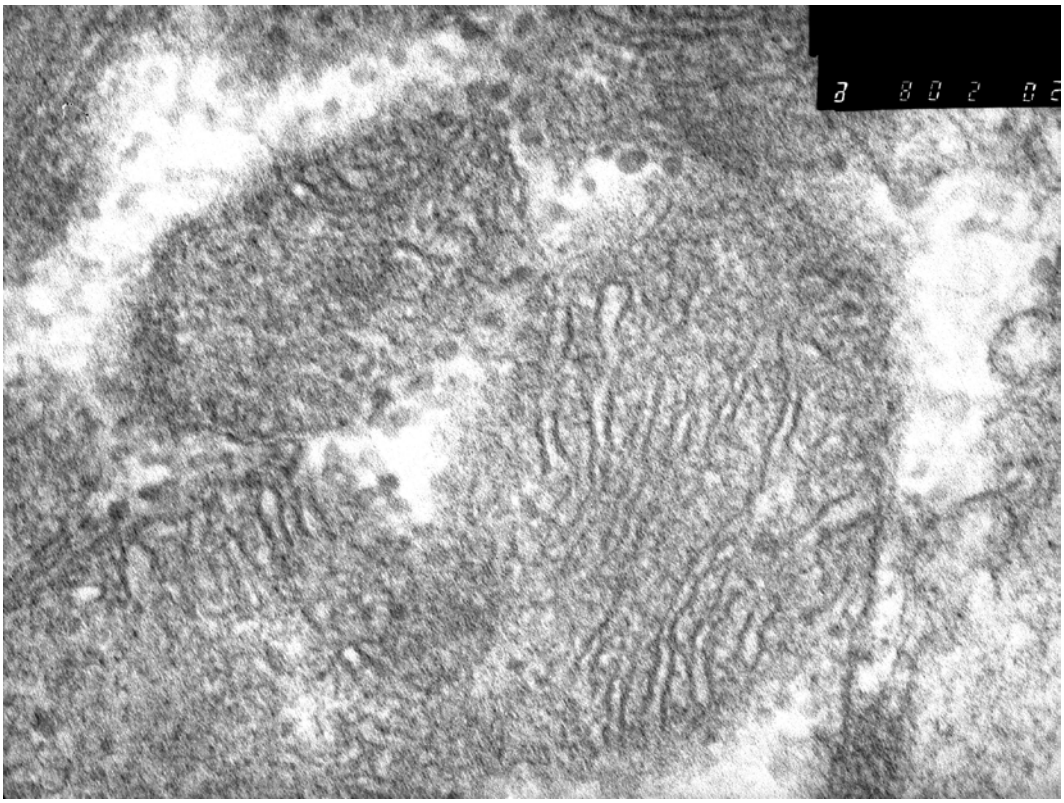


Figure 6B.

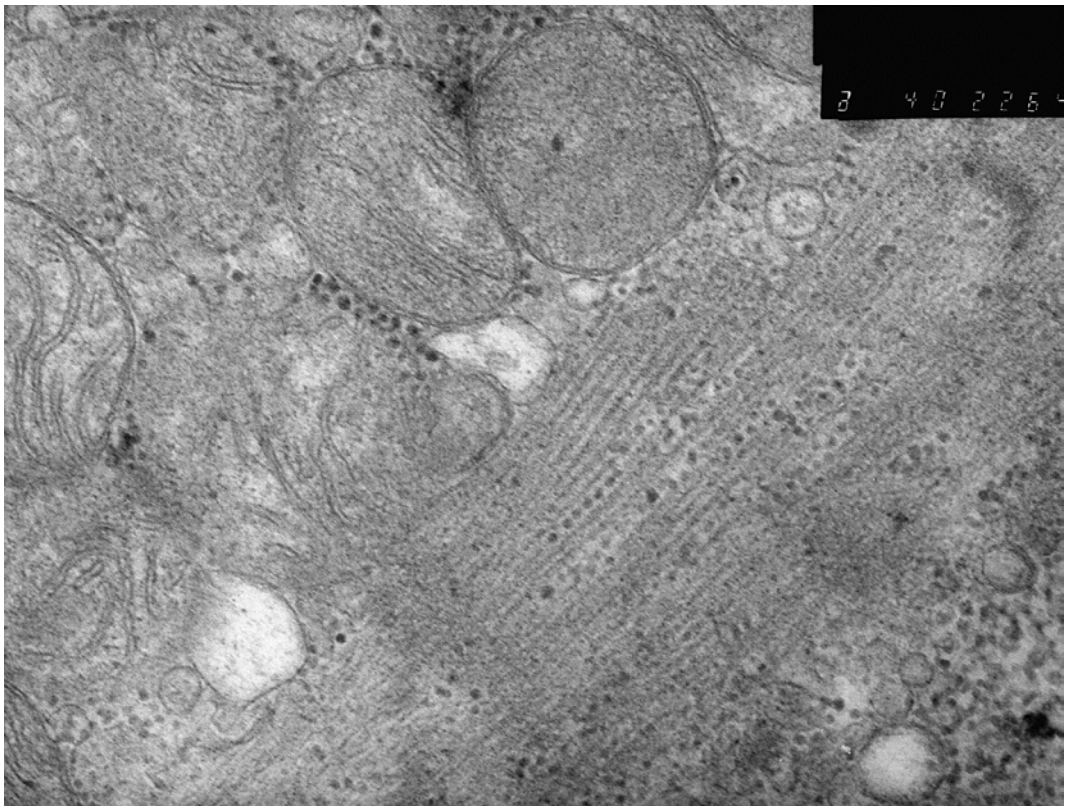


Figure 6C.

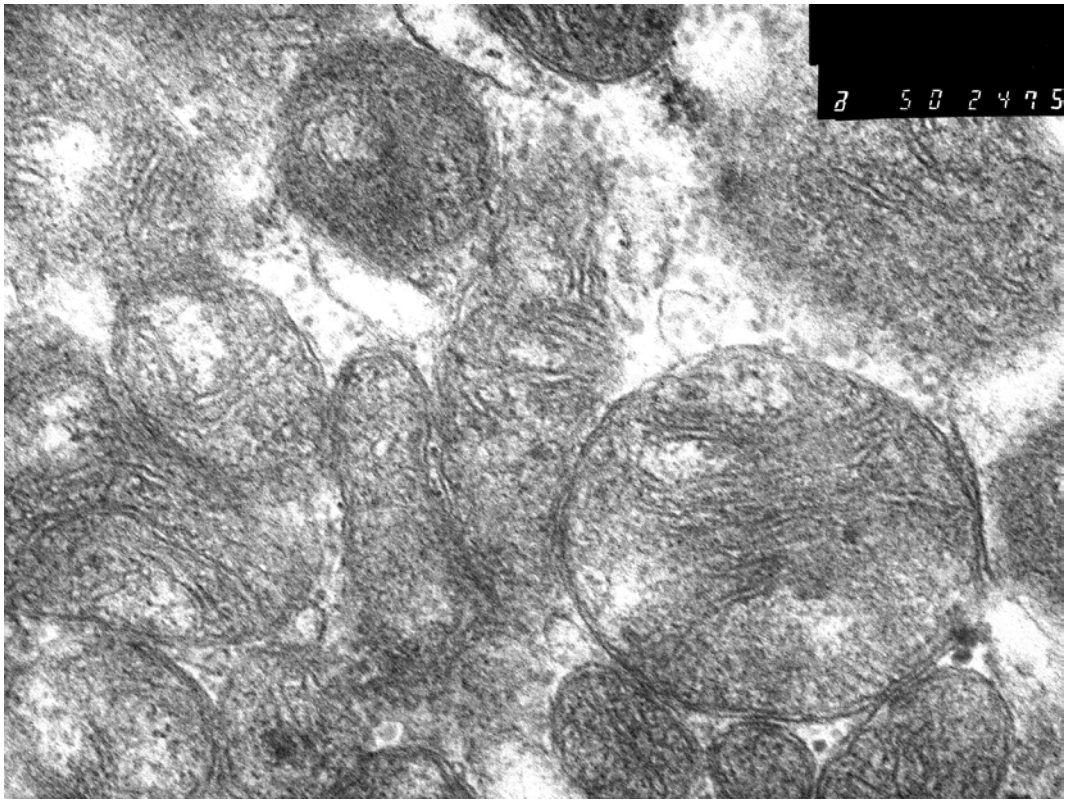


Figure 6D.

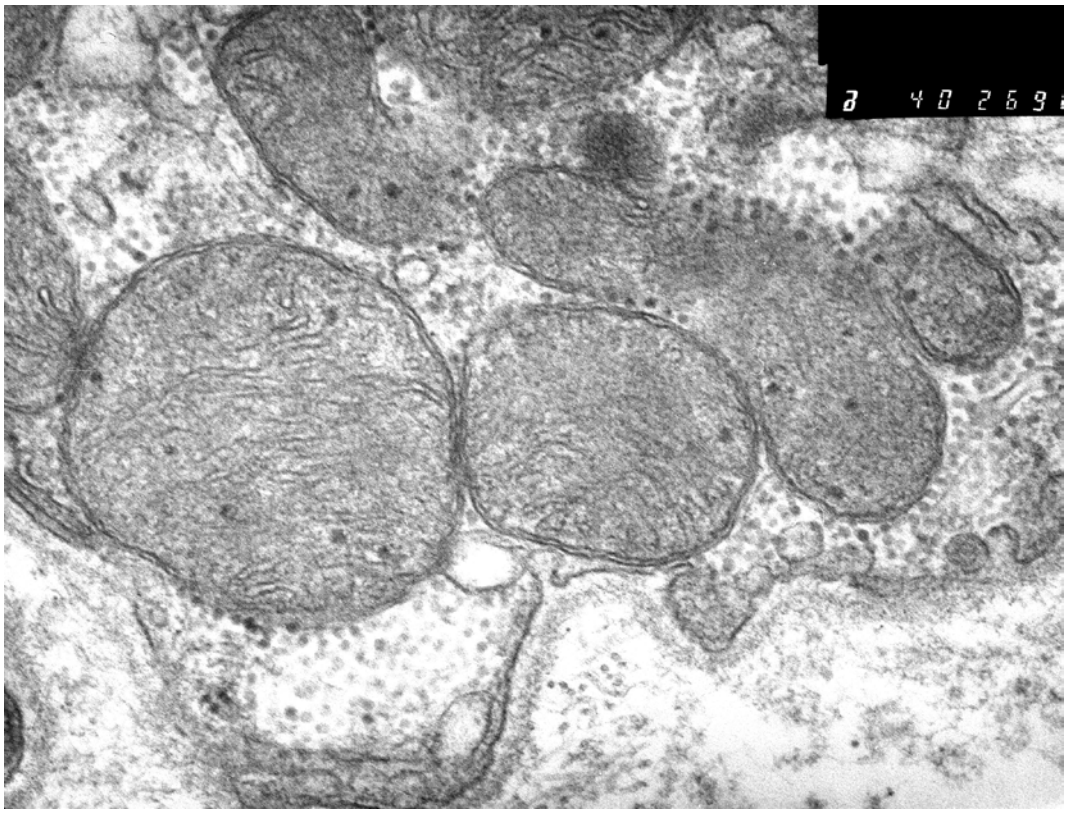


Figure 6E.

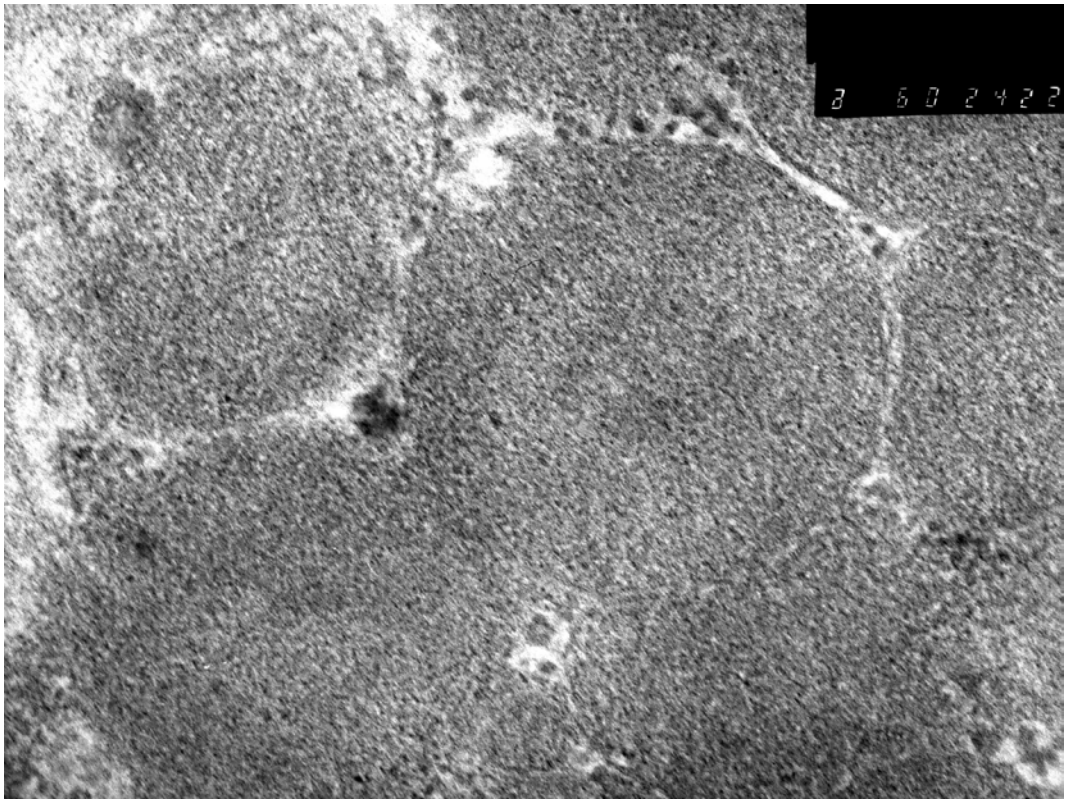


Figure 7A-D. Different degree of intercellular fibrosis.

Figure 7A.

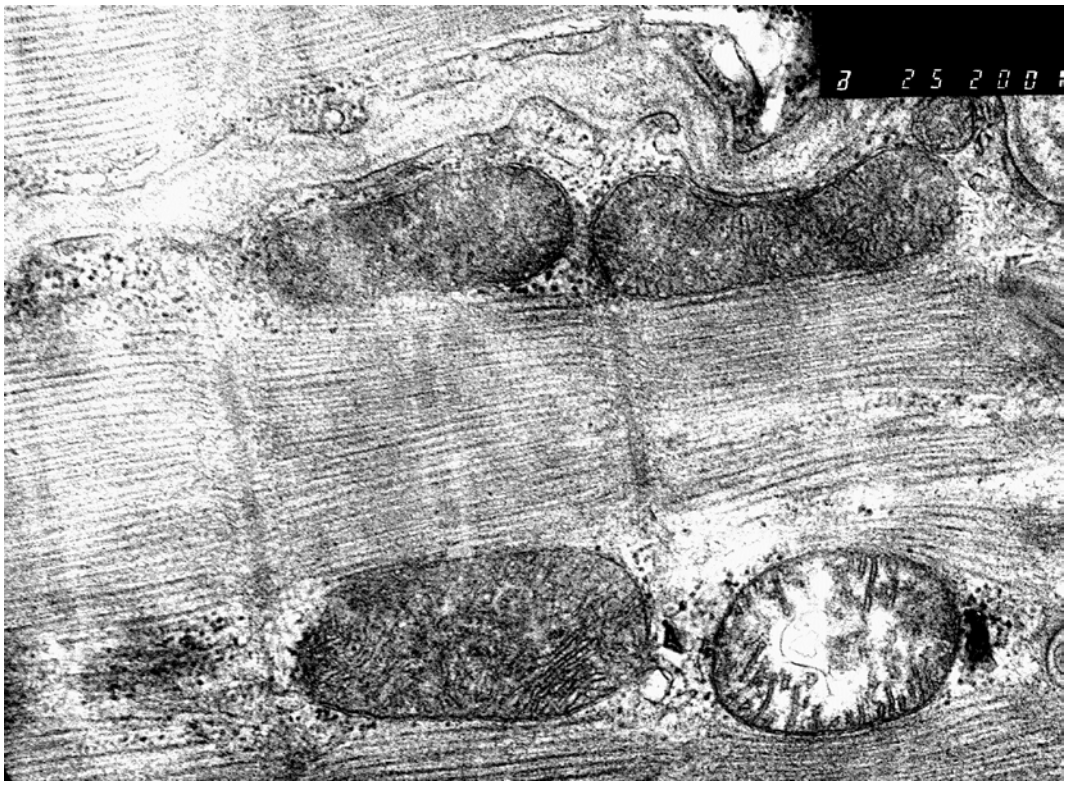


Figure 7B.

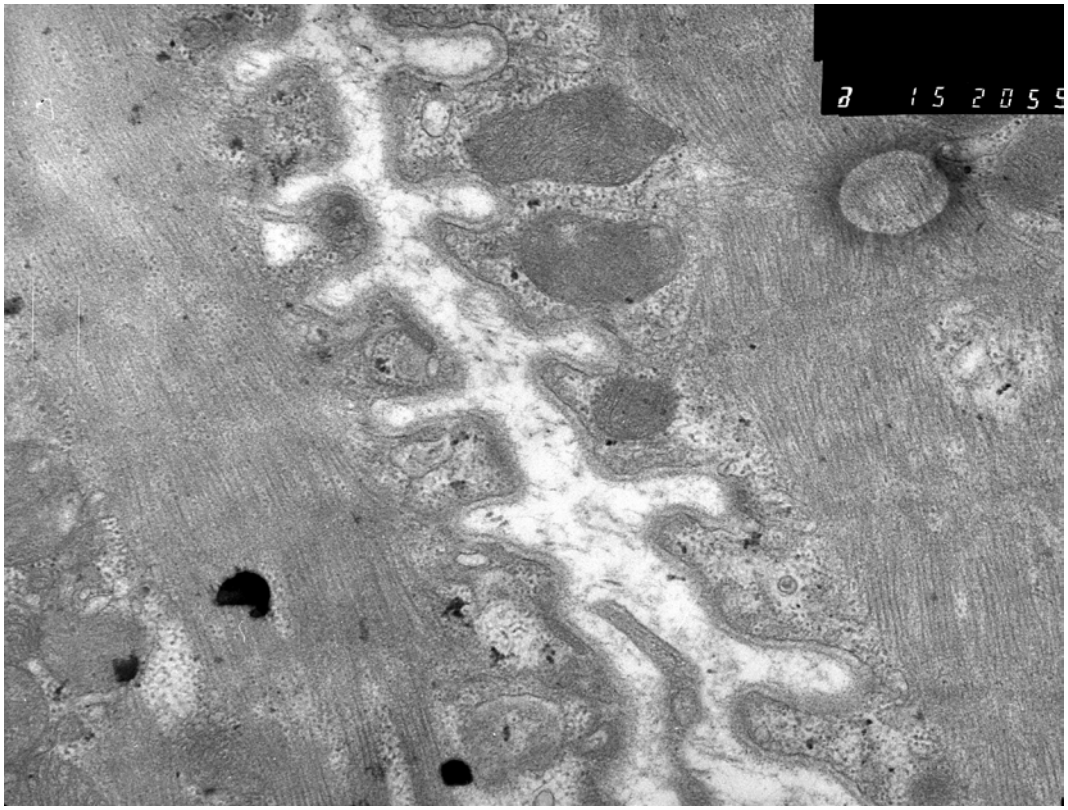


Figure 7C.

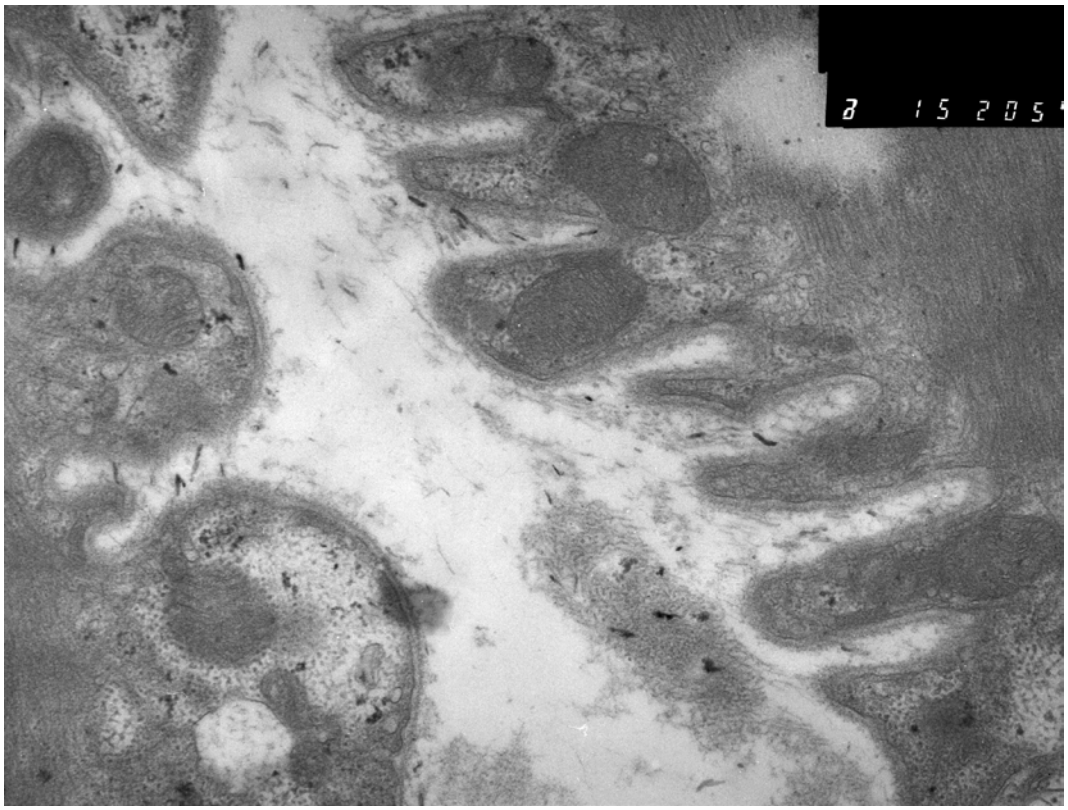


Figure 7D.

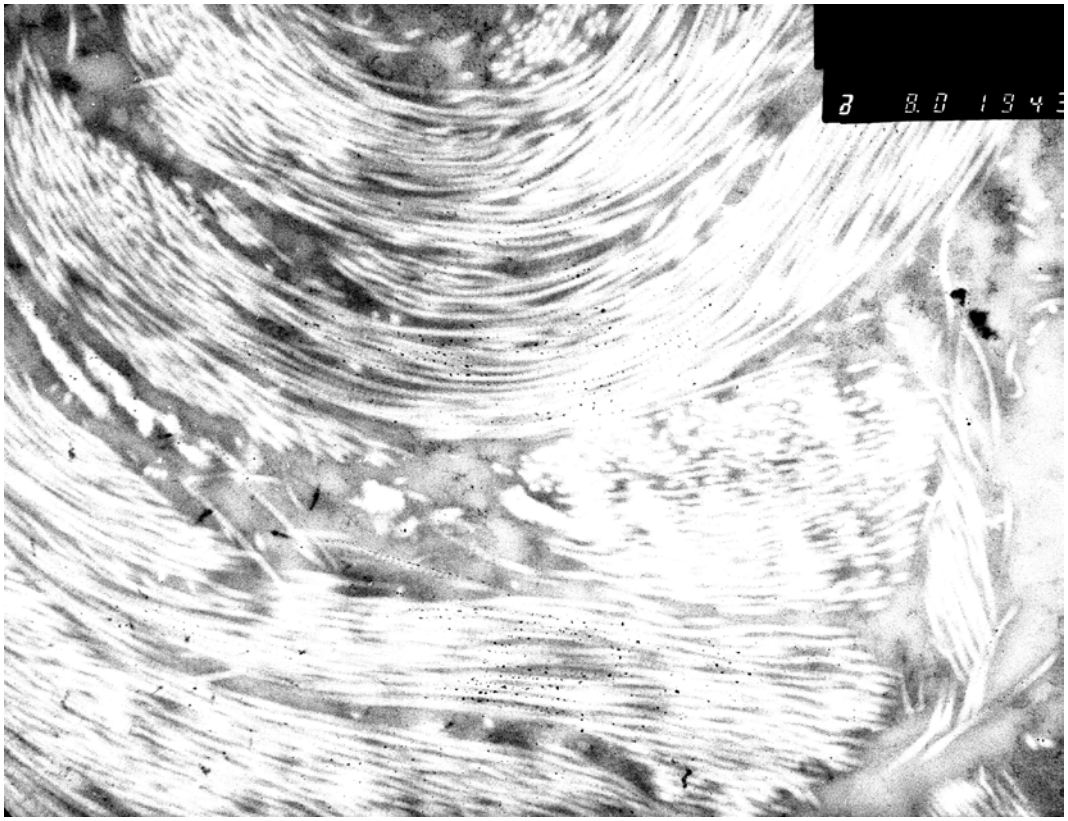


Figure 8. Intercellular space with substrate from thin fibrils and protein.

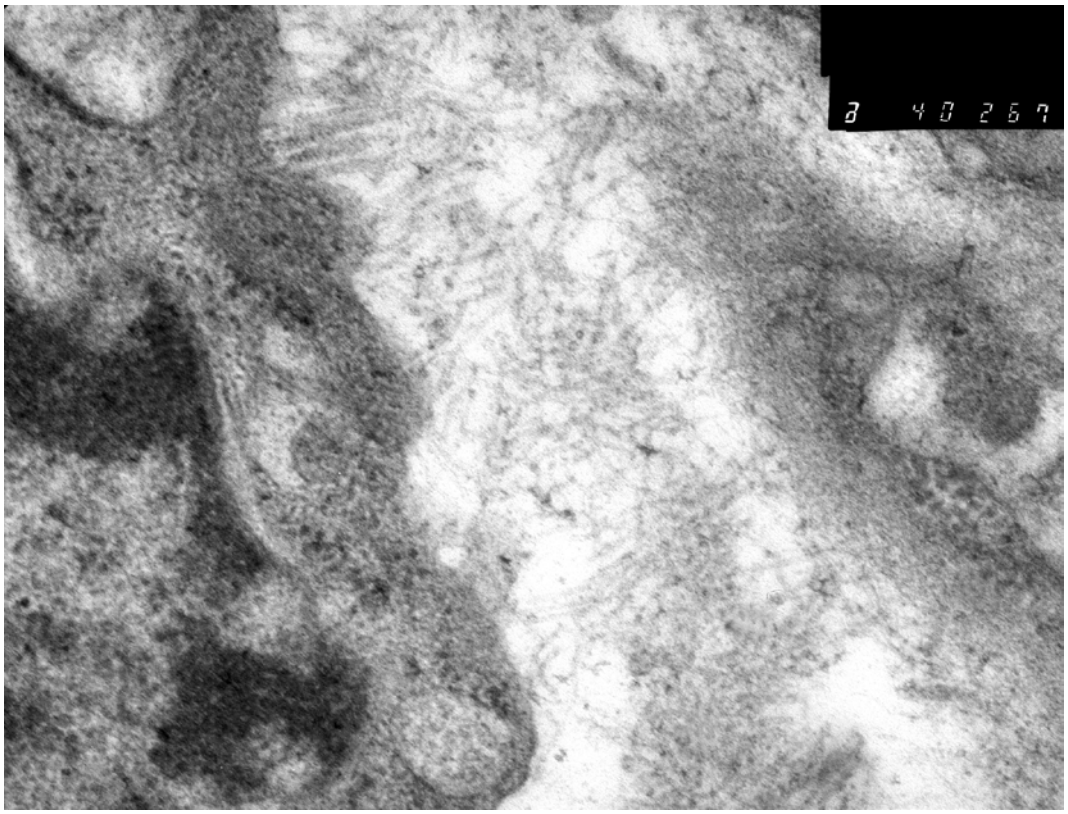


Table 17. Atrial ultrastructural changes and scoring of their expression between sinus rhythm and postoperative atrial fibrillation groups

	SR group (n = 11): RAA (n)/LAA(n)				**Postoperative AF group (n = 9): RAA (n)/LAA(n)**				**P-value for RAA in SR group vs. RAA in AF group**	**P-value for LAA in SR group vs. LAA in AF group**
Scoring	0	1+	2+	3+	0	1+	2+	3+		
Lysis of sarcomers	0/0	4/5	6/4	1/2	0/0	4/3	3/5	2/1	0.588	0.841
Rupture of cell membrane	0/0	5/6	4/4	2/1	0/0	3/2	4/5	2/2	1	0.397
Rupture of mitochondrial wall	0/0	5/6	6/4	0/1	0/0	6/2	2/5	1/2	0.254	0.397
Changes in mitochondrial shape	0/0	6/6	4/3	1/2	0/0	3/4	4/3	2/2	0.592	1
Cristolysis	0/0	6/7	4/3	1/1	0/0	3/2	4/4	2/3	0.592	0.216
Changes of orientation of crists, cristocondensation,	1/1	5/7	4/2	1/1	0/0	4/3	4/3	1/3	1	0.368
Bizarre nuclei	2/1	5/6	3/2	1/2	1/1	2/2	5/4	1/2	0.726	0.607
Granules of glycogen	0/0	5/6	4/5	2/0	0/0	3/3	5/4	1/2	0.841	0.373
Intercellular fibrosis	1/0	6/4	3/5	1/2	1/0	5/4	2/2	1/3	1	0.610
Insertion of adipose tissue	2/2	4/6	4/3	1/0	0/0	6/4	3/4	0/1	0.455	0.440
Insertion of substrate from thin fibrils and protein	3/2	5/6	3/2	0/1	1/1	3/2	5/4	0/2	0.603	0.524

AF – atrial fibrillation, LAA – left atrial appendage, n – number of patients in each group, RAA – right atrial appendage, SR – sinus rhythm.

Table 18. Intensity of ultrastructural changes of the left atrial appendage and right atrial appendage tissue in all evaluated cases

	RAA n (%)				LAA n (%)				
Scoring	**0**	**1+**	**2+**	**3+**	**0**	**1+**	**2+**	**3+**	**P value for RAA vs. LAA**
Lysis of sarcomers	0 (0)	8 (40)	9 (45)	3 (15)	0 (0)	8 (40)	9 (45)	3 (15)	1
Rupture of cell membrane	0 (0)	8 (40)	8 (40)	4 (20)	0 (0)	8 (40)	9 (45)	3 (15)	1
Rupture of mitochondrial wall	0 (0)	11 (55)	8 (40)	1 (5)	0 (0)	8 (40)	9 (45)	3 (15)	0.134
Changes in mitochondrial shape	0 (0)	9 (45)	8 (40)	3 (15)	0 (0)	10 (50)	6 (30)	4 (20)	1
Cristolysis	0 (0)	9 (45)	8 (40)	3 (15)	0 (0)	9 (45)	7 (35)	4 (20)	1
Changes of orientation of crists, cristocondensation,	1 (5)	9 (45)	8 (40)	2 (10)	1 (5)	10 (50)	5 (25)	4 (20)	0.503
Bizarre nuclei	3 (15)	7 (35)	8 (40)	2 (10)	2 (10)	8 (40)	6 (30)	4 (20)	0.75
Granules of glycogen	0 (0)	8 (40)	9 (45)	3 (15)	0 (0)	9 (45)	9 (45)	2 (10)	1
Intercellular fibrosis	2 (10)	11 (55)	5 (25)	2 (10)	0 (0)	8 (40)	7 (35)	5 (25)	0.08
Insertion of adipose tissue	2 (10)	10 (50)	7 (35)	1 (5)	2 (10)	10 (50)	7 (35)	1 (5)	1
Insertion of substrate from thin fibrils and protein	4 (20)	8 (40)	8 (40)	0 (0)	3 (15)	8 (40)	6 (30)	3 (15)	0.26

LAA – left atrial appendage, n – number of patients, RAA – right atrial appendage.

5. DISCUSSION

This is the largest study relating AF following cardiac surgery to intraatrial plasma proinflammatory, prothrombotic and extracellular matrix turnover markers. We observed the following novel findings: (1) vWF levels from the LAA blood are lower comparing to other sampling sites in the patients undergoing CABG, and contrary to our hypothesis, plasma vWF levels – irrespective of sampling site – were not associated with the development of postoperative AF; (2) Higher plasma TF levels were found in the LAA compared to the PB and the LA, especially amongst the patients who developed postoperative AF, but TF levels were not associated with the development of AF after CABG; (3) High hs-CRP levels in the peripheral blood, RAA and LA – and high IL-6 levels in the RAA, LA and LAA – were associated with the development of postoperative AF; and (4) There were regional intracardiac differences in TIMP-1 and the TIMP-1/MMP-9 ratios – but not in MMP-9 levels, and higher intra-cardiac levels of MMP-9 within the LAA were associated with the development of postoperative AF after elective CABG. These differences in prothrombotic, inflammatory and extracellular matrix turnover indices may indicate different local substrate for the development of AF postoperatively.

There is increasing evidence for the contribution of inflammation to the pathogenesis of AF [21 – 23, 26 – 27, 192, 400], and cardiac surgery and cardiopulmonary bypass can themselves cause an inflammatory response and oxidative stress, although this may not necessarily relate to the development of AF [164, 184]. Is there any preexisting local low-grade inflammatory process, which exacerbates in response to cardiac surgery with cardiopulmonary bypass and leads to the development of postoperative AF? Nevertheless, although plasma hs-CRP and IL-6 are established markers of inflammation in 'chronic' AF, their role in predicting the development postoperative AF is controversial. Some contend that arrhythmia events coincide with the highest levels of CRP, and

that higher preoperative hs-CRP, but not IL-6, is associated with AF after CABG [185 – 186]. In a study by Lo et al high baseline CRP levels were associated with higher risk of the development of AF after both on-pump and off-pump CABG operations [185]. Higher preoperative levels of hs-CRP, but not of IL-6, were found associated with the occurrence of AF after elective CABG surgery in a small study from Turkey [186]. Perioperative monocyte CD11b upregulation, an increase in monocyte and neutrophils count obtained after aortic-cross-clamp release were reported in patients developed AF after on-pump cardiac surgery, but in contrast to other studies, preoperative plasma CRP levels and perioperative myeloperoxidase activity did not sociated with postsurgery AF [194]. There was not found any significant association between baseline CRP levels and the occurrence of postsurgery AF in a study by Hogue et al [196]. In a study by Pretorius et al 21 biomarkers (different proinflammatory, prothrombotic and profibrotic indices) were measured in peripheral blood obtained preoperatively and immediately after CPB in 253 consecutive patients undergoing elective on-pump cardiac surgery, and only PAI-1 – well known as an acute phase reactant – was found as independent predictor for the development of postsurgery AF [198]. The authors suggested that induction of inflammation during cardiac surgery, but not preexisting systemic inflammation process, might contribute to the development of postoperative AF [194, 196, 198]. The contrary studies were also published. In a study by Ahlsson et al. neither preoperative plasma CRP levels, nor postoperative CRP levels were significantly different between patients developed postsurgery AF comparing to those remained in SR [197].

In the present study, we found significantly higher preoperative plasma CRP levels in the PB, RAA and LA of patients with postoperative AF although CRP levels did not significantly associate with other clinical factors in multiple stepwise regression analysis. Plasma IL-6 levels were significantly higher in the RAA, the LA and the LAA of patients with postoperative AF. Multivariate analysis showed that only postoperative AF was associated with higher IL-6 levels in both atrial

appendages. The local proinflammatory milieu is consistent with experimental studies showing that atrial inflammation is associated with an increased inhomogeneity of atrial conduction and AF duration, and antiinflammatory therapy decreased the inhomogeneity in electrical conduction and shortened the duration of AF [183].

The present contribution to this debate is that higher preoperative plasma CRP levels in the peripheral circulation (confirming other data [186, 188 – 190, 194]), but also in intracardiac blood (RAA and LA) predict postoperative AF. Although plasma IL-6 levels were significantly higher in the RAA, the LA and LAA of patients with postoperative AF, peripheral venous IL-6 levels were not predictive, again confirming other data [186]. Only one small study (included 54 patients undergoing elective CABG) reported a significant relationship between elevated preoperative peripheral IL-6 levels with the occurrence of postoperative AF [190].

Of note, all our patients undergoing CABG surgery suffered from severe coronary artery disease, and coexistence of an inflammatory process alongside coronary artery atherosclerosis may be pathogenetically related [401]. However, it is unclear why the degree of postoperative inflammatory response differs between patients undergoing the same kind of heart surgery, and – as is well recognized – AF does not develop in all patients. The existence of a different genetic predisposition of inflammatory response to cardiac surgery and the development of postoperative AF have been proposed [199].

Several human histological studies on the RAA samples have demonstrated the existence of structural atrial substrate, which predisposes development of AF after cardiac surgery [129 – 130, 135, 139, 144], and most were conducted in patients undergoing elective CABG surgery [129 – 130, 139, 144]. More pronounced myolysis and apoptosis was noted in postoperative AF atrial myocardium [129 – 130, 139], whilst Mariscalco et al found increased atrial fibrosis [34]. CRP takes part in the elimination of apoptotic cells [402], whereas lost myocardial cells are

replaced with fibrotic tissue, leading to structural atrial remodeling. Plasma CRP might also contribute to the local atrial inflammatory process itself, promoting local complement pathway activation and myocardial damage [403].

The LA is the site of 'origin' of lone AF and AF related to structural heart disease [123]. Is the same for the poscardiacsurgery AF? Electrophysiologically this question has not been investigated, and previous studies that have revealed histological atrial substrate contributing to the development of postoperative AF, were performed most on RA samples. Moreover, the relationship between histological findings and plasma proinflammatory and prothrombotic markers has not been studied, nor regional differences between the systemic circulation, and right and left atria.

Key molecules in the process of tissue remodelling are MMP-9 and its regular tissue inhibitor of metalloproteinases [26 – 27, 201, 205]. MMPs and TIMPs are involved in the mediation of cell-to-cell adhesion, cell migration, invasion, proliferation and apoptosis, tissue remodeling, mediation of angiogenesis, cardiovascular development and diseases [201]. The early increase in MMP activity during cardiac overload has been reported [404]. Hemodynamic factors might be contributed to atrial fibrosis and remodeling [204] and several publications have linked the MMP/TIMP system to atrial remodeling of fibrillating human atria in the setting of CHF [205], as well as in AF unrelated to CHF [27]. Recently was demonstrated a pattern of MMP-9 influence on atrial remodelling in the setting of arterial hypertension [207], Corradi et al reported higher MMP-9 and MMP-2 levels in LA posterior wall in patients with valvular AF [208]. Huxley et al reported the prospective relationship between elevated levels of serum MMP-9 and risk of incident AF [209]. Case-control studies of genetic polymorphisms that alter MMP-9 production and activity have also provided some support of a role of MMP-9 in the pathophysiology of AF [210 – 211]. In our study variation in TIMP-1 and MMP-9 levels in blood from different cardiac chambers has been found, reminiscent of the study by Mukherjee et al

[205], who found increased expression of MMP-1 and MMP-9 in the RA and LA myocardial tissue respectively in congestive heart failure patients with AF compared to those in SR. Moreover, increased gene expression of MMP-9 in the LAA compared to the RAA was demonstrated recently in valvular AF [405]. We also found higher plasma MMP-9 levels only in the LAA of patients who developed AF after CABG compared to those who remained in SR.

vWF is an established marker of endothelial dysfunction/damage and raised levels (as are present in coronary artery disease, stroke, AF, and many other vascular conditions) predict adverse cardiovascular outcome [406 – 408]. There is evidence, that endothelial dysfunction, as was demonstrated by impairment of flow mediated dilation and raised levels of vWF and soluble E-selectin, is present in AF [409]. Recently, Scridon et al demonstrated an association between the clinical evolution of AF and the progression of endothelial dysfunction [410]. It is still unclear if endocardial dysfunction/damage precedes the development of AF, although Alonso et al reported increased risk of incident AF associated with higher levels of vWF in 14858 individuals with mean follow-up of 16.8 years, but the study had a limitation due to imprecise documentation of AF episodes [411]. The endocardial dysfunction/damage has not been understood in patophysiology of postoperative AF. Increased levels of vWF and other prothrombotic molecules (such as TF, soluble thrombomodulin and fibrinogen) in AF are established and may be related to the increased risk of thromboembolism and stroke in this group of patients [28, 248, 412 – 414]. The increased levels of plasma vWF were found in patients with AF and spontaneous echocontrast [415]. In addition, plasma levels of vWF have been found higher in patients with mitral valve disease compared to healthy controls, in patients with lone AF, and in patients with advanced endocardial alterations in the LAA compared to those with minimal changes [223, 228, 240, 416]. We were therefore surprised to find that neither plasma vWF nor plasma TF were associated with postoperative AF, although vWF nearly did so. This is reminiscent of the study by Li-Saw-Hee et al [32]

where authors were unable to find any significant differences of prothrombotic markers or indices of endothelial dysfunction/damage (soluble thrombomodulin, vWF) between peripheral arterial, venous blood and both atria in 25 patients with AF secondary to mitral stenosis. It can be therefore suggest that the general hypercoagulability profile in CABG patients does not predict short-term AF.

The present study has a number of limitations. It is of note that all of patients were observed by continuous ECG monitoring only within the first 24 – 48 hours after CABG – many postoperative AF episodes are short and self-terminating, with a peak of incidence on the second day following cardiac surgery, and AF may be asymptomatic in some individuals. Thus, the possibility remains that some occurrences of postoperative asymptomatic AF were undetected in the present patient population. Secondly, bloods from different sampling sites were not collected simultaneously at precisely the same time point, which would have been logistically impossible. Samples from the LAA were taken a few minutes later after cardioplegia had been performed. This might result in greater haemodilution and lower concentrations of biomarkers at that particular sampling site. Whilst there were significantly lower levels of plasma vWF, hs-CRP, TIMP-1 and MMP-9 (in SR group) in the LAA compared to other sites, there were significant differences between various sampling sites for IL-6 levels, and plasma TF concentrations were significantly higher in the LAA samples. The reasons why the LAA locus has provided the best discriminative data are unclear. We hypothesised that it may reflect tissue expression of the same markers, but we failed later to prove that (partially except on vWF). As it has been discussed above, there are controversial data about the influence of different biomarkers on postoperative AF, or even on the AF at all. A possible explanation for these discrepant findings may be due to differences in blood collection and storing. For example, the level of MMP-9 has been shown to be higher in serum than in plasma [417] and in samples treated with the ethylene-diamine-tetraacetic acid (EDTA) compared to those treated with citrate [418].

Finally, it is clear that presented data are derived from 'traumatic' AF, and from one of the several different types of 'chronic' AF [400] so may not be relevant to wider AF community.

This study is one of the largest investigating tissue expression of pathophysiologic markers in relation to postoperative AF. It shows, for the first time, that more intense expression of vWF by LAA tissue was a significant predictor of AF after CABG. Although sampling blood from a peripheral vein may reflect intracardiac levels [32], and sampling intracardiac blood may help predict those who will develop AF after CABG, the degree to which atrial tissues per se predict AF was previously unknown. Although IL-6, MMP-9 and TIMP-1 expression by RAA and LAA epicardium was stronger than expression by endocardium or cardiomyocytes, these differences all failed to predict postoperative AF. The results of present study on immunohistochemical assessment of atrial tissue point towards a possible role of endothelial damage/dysfunction (as reflected by vWF changes) in the pathogenesis of postoperative AF.

There is an increasing evidence for the contribution of inflammation [20, 22 – 23, 28, 305, 400], thrombosis [28 – 32] and abnormal remodelling [24 – 27, 210, 419] to the pathogenesis of AF, and although cardiac surgery and cardiopulmonary bypass surgery can themselves cause an inflammatory response, this may not necessarily relate to the development of AF per se [6, 10 – 13, 15]. It has been discussed that thrombogenesis and the proinflammatory state in AF both closely related to endothelial dysfunction [243]. There has been a greater focus on more early and comprehensive management of AF [400], with a recommendation in current management guidelines for early interventions with so-called 'upstream therapy' in the presence of cardiovascular risk factors for the development of AF [305] that could potentially influence these pathogenetic processes (inflammation, remodeling, etc.).

Several histologic studies have tested the hypothesis that some structural changes to extracellular matrix metalloproteins or inflammation in cardiac chambers and

tissues (such as the LAA and RAA) are associated with AF [27, 93, 108 – 109, 205, 420]. For example, atrial biopsy specimens in lone AF showed signs of myocarditis in 66 % of patients [108]. Polyakova et al [420] studied the RAA and the right atrial free wall tissues in patients with history of AF and reported that atrial fibrosis in AF is characterized by severe alterations in collagen I and III synthesis/degradation associated with disturbed MMP/TIMP systems. Boldt et al [109] reported that both lone and valvular AF are associated with atrial fibrosis. Xu et al showed that AF in heart failure patients was associated with extracellular matrix remodeling in both atria [93]. In contrast, Anné et al in a small study with human LAA and RAA tissues did not found any association between atrial fibrosis (described as down-regulation of MMPs) and AF [206]. Some studies have specifically investigated structural and cellular histologic appearances in relation to postoperative AF [130, 138 – 139, 144], but immunohistochemical staining of vWF, inflammation or extracellular matrix remodelling markers were not reported. Of note, most of published studies were tested only the RAA. For example, Ak et al [130] reported that the degree of myolysis and increased apoptotic pattern in the right atrial myocardium are significant predictors for the development of postoperative AF. Indeed, atrial histology showed degenerative changes that may correlate with advanced age and left atrial enlargement [139]. Nakai et al [144] reported quantitative assessment of atrial fibrosis with Sirius red stain, and found that age-related atrial fibrosis rather than cellular hypertrophy may be important in the pathogenesis of AF after CABG. Grammer et al reported in a small study that a shift in right atrial collagen expression levels in favour of collagen type I was linked to the occurrence of AF in patients undergoing different type of cardiac surgery [138].

VWF is an established plasma marker of endothelial damage/dysfunction, and increased levels predict adverse cardiovascular outcomes [406]. There is sufficient evidence that AF is associated with impairment of endothelial function [421 – 423]. In this plasma marker study, neither vWF level nor TF (another

marker of endothelial dysfunction) level was associated with postoperative AF, suggesting that the general hypercoagulability profile in CABG patients did not predict short-term AF. The discrepancy between the inability of plasma vWF to predict postoperative AF and the ability of tissue expression to detect postoperative AF may be a result of the fact that any vWF shed by a perturbed endothelium would be immediately diluted by flowing blood, whereas cell-bound vWF, as detected by immunohistochemistry, would be expected to have a higher local concentration. It was pursued in an exploratory analysis, relating the expression of vWF by the LAA and RAA to plasma vWF (Table 16). Levels of plasma vWF increased significantly in parallel with LAA expression only in the combined group of subjects. We do not interpret this as suggesting that the increase in plasma vWF is attributable to expression by LAA alone, but it may be that increased LAA tissue expression reflects whole body increased production of vWF. Nevertheless, it has been previously reported that peripheral vWF levels could be correlated with severity of endocardial damage, as visualized by scanning electron microscopy of LAA sections obtained during MVS [240]. In a further non-operative study, changes in plasma vWF levels and ADAMTS13 levels have been related to left atrial remodelling in AF [424]. Furthermore, increased vWF and TF expression in atrial endothelium have been associated with thromboembolism in a cohort of patients with non-valvular AF [247]. Also increased expression of vWF in atrial endocardium was associated with enlarged left atrium in mitral valve disease [244], but no relationship with the development of new postoperative AF was investigated. Indeed, increased vWF expression in the endocardium may represent a local predisposing factor for enhanced thrombogenesis, given that the greatest vWF expression correlated with grade of thrombus formation as well as with associated mitral valve disease [243].

As mentioned above, we are unaware of any published work relating immunohistochemical tissue expression staining of vWF (and other

pathophysiologic markers) to the development of postoperative AF. A possible role of endothelial damage/dysfunction (as reflected by vWF expression changes) in the pathogenesis of postoperative AF and its complications merits further study, and – as implied earlier – may be therapeutic implications, with drugs that have beneficial effects on the endothelium, such as angiotensin-converting enzyme inhibitors and statins, which are often considered as 'upstream therapy' for AF management in patients with cardiovascular risk factors [305, 400]. Indeed, (systemic) plasma vWF level is related to cardiovascular diseases and increases with age [406] (and, accordingly, is attracting attention as the potential target of a pharmaceutical agent [425]), and our patients who developed postoperative AF were slightly older than those who remained in SR. Interestingly, Seljeflot et al recently published a study on elderly AF patients who had significantly impaired endothelial function assessed by increased levels of vWF, and more pronounced by high levels of ADAM [426]. Although there is plausible evidence that plasma vWF directly promotes thrombosis [406], the presented study cannot conclude whether or not the increased expression of vWF by atrial tissue directly contributes to the increased risk of thrombosis present in AF, or, indeed, whether the increased expression of vWF directly contributes to the development of AF. It may be that increased expression of vWF is simply non-specific marker of the risk of developing AF, and that it has no major pathophysiologic consequences. Whether increased expression of vWF in atrial tissue presents a similar pathology requires confirmation in a larger population, although the 'non-AF' group of our study was broadly similar to the 'postoperative AF' group with regard to associated comorbidities and concomitant drug therapies.

The present study is limited by its modest size, although 30 patients with postoperative AF and immunohistochemical tissue expression staining represent the largest published series in the literature. Although immunohistochemistry is a very powerful method for detecting localization of proteins within tissue sections, it have to be recognized that it is not very suitable for quantification of protein

concentrations, which is beyond the scope of the present study objective. More detailed mechanistic analyses would involve a substantially more complicated study, which would require complex molecular biology investigations with western blotting or additional quantitative analyses to confirm the present observations.

Indeed, given the relatively small numbers, it has been opted for a simple cross-sectional comparison of those developing postoperative AF with those free of AF, and has not related the histologic changes to the temporal distribution of incident AF, etc. As mentioned above, all of patients were observed by continuous ECG monitoring only within the first 24 – 48 hours after CABG. Thus, the possibility remains that some occurrences of postoperative asymptomatic AF were undetected in the present patient population. This study is also underpowered to confidently determine detailed predictors of postoperative AF, based on age, comorbidities (for egsample, extent of coronary disease, cardiac function, and left atrial size), and gender. Tissue samples were also examined and scored independently by two board-certified consultant histopathologists, rather than with imaging software. However, the agreement between observers (kappa = 0.58), although 'moderate', is close to 'good' (defined by statistical convention as a kappa of ≥ 0.61) [399]. Finally, our data are derived from 'traumatic' surgery-related AF, and may not be relevant to the wider AF population.

Our EM study is presented as a descriptive study. We found marked ultrastructural changes in both atrial appendages of the whole cohort of 20 patients undergoing elective CABG.

Goldsmith et al described ultrastructural changes in both atrial appendages from 35 patients with severe mitral stenosis [240]. They found that advanced endocardial changes assessed by scanning EM were more frequently seen in the endocardium of the LAA comparing with the RAA (31% vs. 6%). Contrary to this study, we did not find any significant difference in ultrastructural changes between both appendages in patients with severe coronary artery disease. It

means that mitral valve stenosis contributes to more pronounced ultrastructural remodeling of the LA than coronary artery atherosclerosis.

There are only few small studies on atrial ultrastructural changes relating to the development of postoperative AF. The published data are discrepant and discribe atrial ultrastructural changes in most cases only on the RAA. Mariscalco et al performed EM assessment of the RAA from 9 patients undergoing CABG [139]. They found an association between fibrosis, myocyte vacuolization, nuclear derangement and the incidence of postoperative AF. Ad et al examined the RAA tissue from 60 patients undergoing elective CABG [129]. Myolysis and lipofuscin granules were found to be independent findings associated with the development of postoperative AF. Authors did not find any mitochondrial changes on EM, but it is not evident how many cases they examined by EM (researches noted that EM was performed not on all samples). Recently, Garcia et al described ultrastructural changes of the RAA in patients undergoing CABG, and also found postoperative AF to be associated with lipofuscin deposits and autophagic vesicles [147].

Cosgrave et al examined the RAA tissue samples from 94 patients undergoing CABG and related findings to the development of postoperative AF [143]. They did not find any correlation between the ultrastructural changes of the RAA tissue and postoperative AF. Similarly, we also did not revealed any association between the RAA ultrastructural changes and postoperative AF. Moreover, we did not find any association between the LAA ultrastructural abnormalities and the incidence of postoperative AF.

Of note, our study is too small by its size and assessment of atrial microphotographs was performed only by one pathologist.

In conclusion, data from our work suggest that intracardiac inflammatory environment that is manifest perioperatively may predispose to the development of postoperative AF. This intracardiac inflammatory state was reflected by increased intracardiac hs-CRP and IL-6 levels. Differences of intraatrial levels

of hs-CRP, IL-6, MMP-9 may indicate local substrate abnormalities contributing to the development of AF after CABG surgery. Moreover, data from our immunohistochemistry study point towards a possible role of endothelial damage/ dysfunction (as reflected by vWF changes) in the pathogenesis of postoperative AF. We found marked ultrastructural changes in both atrial appendages in patients undergoing CABG, but we are not able to associate it to the development of AF after cardiac surgery.

6. CLINICAL IMPLICATION

Our observations on an intracardiac inflammatory state which was also reflected by increased peripheral hs-CRP levels in our patients would have implications for anti-inflammatory interventions, as supported by several small interventional studies showing prevention of post-CABG AF with (for example) steroids [427], vitamin C [174], omega-3 fatty acids [378] and statins (due to supposed pleotropic anti-inflammatory effect) [354].

7. NOVELITY

This is the largest study relating AF following cardiac surgery to intraatrial plasma proinflammatory, prothrombotic and extracellular matrix turnover markers. The present study is one of the largest investigating tissue expressions of pathophysiologic markers in relation to the development of postoperative AF. It shows, for the first time, that more intense expression of vWF by LAA tissue was a significant predictor of AF after on-pump CABG.

8. CONCLUSIONS

1. Levels of plasma vWF, TF, hs-CRP and indices of extracellular matrix turnover (MMP-9 and TIMP-1) differ inbetween various intracardiac sampling sites.
2. Higher preoperative plasma hs-CRP levels in the peripheral and intracardiac (the RAA and LA) blood predict the development of AF after on-pump CABG surgery.
3. Higher preoperative plasma IL-6 levels in some intracardiac chambers (the RAA, the LA and the LAA) but not in the peripheral circulation are associated with the occurrence of AF after on-pump CABG surgery.
4. Higher preoperative plasma MMP-9 concentration in the LAA is associated with the AF after on-pump CABG surgery.
5. An increased expression of vWF by the endocardium of the LAA is a risk factor for the development of AF after elective on-pump CABG surgery.
6. Tissue expression of vWF, TF, IL-6, MMP-9 and TIMP-1 by the LAA does not differ significantly from tissue expression of the same markers by the RAA.
7. Both atrial appendages of patients undergoing on-pump CABG show pronounced ultrastructural changes.

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10. PUBLICATIONS RELATING TO DOCTORAL DISSERTATION

1. Diana Kaireviciute, Audrius Aidietis and Gregory Y.H. Lip. Atrial fibrillation following cardiac surgery: clinical features and preventative strategies. European Heart Journal 2009; 30(4): 410-425.
2. Diana Kaireviciute, Audrius Aidietis, Gregory Y.H. Lip. Pathophysiological Insights into Atrial Fibrillation Following Cardiac Surgery: Implications for Current Pharmaceutical Design. Current Pharmaceutical Design 2009; 15(29): 3367-3383.
3. Kaireviciute D, Blann AD, Balakrishnan B, Lane DA, Patel JV, Uzdavinys G, Norkunas G, Kalinauskas G, Sirvydis V, Aidietis A, Lip GY. Characterisation and validity of inflammatory biomarkers in the prediction of post-operative atrial fibrillation in coronary artery disease patients.Thrombosis and Haemostasis 2010; 104(1): 122-127.
4. D. Kaireviciute, G.Y.H. Lip, B. Balakrishnan, G. Uzdavinys, G. Norkunas, G. Kalinauskas, V. Sirvydis, A. Aidietis, U. Zanetto, H. Sihota, M. Maheshwari, A.D. Blann. Intra-Cardiac Expression of Markers of Endothelial Damage/ Dysfunction, Inflammation, Thrombosis and Tissue Remodeling, and the Development of Post-Operative Atrial Fibrillation. Journal of Thrombosis and Haemostasis 2011; 9: 2345-2352.

Theses:

1. D. Kairevičiūtė, B. Balakrishnan, J. Patel, D. Lane, G. Uždavinys, G. Norkūnas, G. Kalinauskas, V. Sirvydis, A. Aidietis, G. Lip. Abnormal intracardiac C-reactive protein and interleukin-6 levels predict the development of atrial fibrillation following coronary artery bypass grafting surgery // European heart journal. 2008, vol. 29, suppl. 1: ESC Congress 2008, Munich, Germany, 30 August - 3 September 2008: abstracts, p. 296.

2. D. Kairevičiūtė, B. Balakrishnan, A. Blann, D. Lane, G. Uždavinys, G. Norkūnas, V. Sirvydis, A. Laucevičius, A. Aidietis, G. Lip. High matrix metalloproteinase-9 levels within the left atrial appendage are associated with the development of postoperative atrial fibrillation after coronary artery bypass grafting surgery // European heart journal. 2008, vol. 29, suppl. 1: ESC Congress 2008, Munich, Germany, 30 August - 3 September 2008: abstracts, p. 711.
3. D. Kairevičiūtė, B. Balakrishnan, A. Blann, D. Lane, G. Uždavinys, G. Norkūnas, V. Sirvydis, G. Marinskis, A. Aidietis, G. Lip. Plasma von Willebrand factor levels and the development of postoperative atrial fibrilation in patients undergoing coronary artery bypass grafting: do intracardiac levels matter? // European heart journal. 2008, vol. 29, suppl. 1: ESC Congress 2008, Munich, Germany, 30 August - 3 September 2008: abstracts, p. 218.

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LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2006-02-03 Nr.: 2

Biomedicininio tyrimo pavadinimas:
Protrombozinės būklės esant ne vožtuviniam prieširdžių virpėjimui tyrimas: prokoaguliacinų citokinų kiekio intraprieširdiniame kraujyje ir prieširdžių endokarde palyginimas pacientų, sergančių prieširdžių virpėjimu bei esant sinusiniam ritmui ir kuriems atliekama aorto-vainikinių jungčių suformavimo operacija

Protokolo Nr.: **2**
Versija Nr.: **3.1**
Data: **2005 m. lapkričio 30 d.**

Asmens informavimo ir informuoto asmens sutikimo formos (tiriamosios ir kontrolinės grupės pacientams):
Versija Nr.: **3.1**
Data: **2006 m. sausio 23 d.**

Pagrindinis tyrėjas: **Doc. Audrius Aidietis**

Biomedicininio tyrimo vieta:
Įstaigos pavadinimas: **Vilniaus universiteto ligoninės Santariškių klinikos Kardiologijos ir angiologijos centras**
Įstaigos adresas: **Santariškių 2, Vilnius**

Leidimas išduotas Lietuvos bioetikos komiteto posėdžio, įvykusio **2006 m. sausio 24 d.**, sprendimu.

Lietuvos bioetikos komiteto biomedicininių tyrimų ekspertų grupės nariai			
Nr.	Vardas, Pavardė	Veiklos sritis	Dalyvavo posėdyje
1	Gyd. Gintarė Breivienė	pediatrija	taip
2	Gyd. Vytautas Čepulis	onkologija	taip
3	Doc. Eugenijus Gefenas	bioetika	taip
4	Doc. Zita Liubarskienė	filosofija	taip
5	Dr. Andrius Narbekovas	teologija	taip
6	Prof. Algimantas Raugalė	pediatrija	taip
7	Doc. Krescentius Stoškus	filosofija	taip
8	Gyd. Vytautas Tutkus	mikrochirurgija	taip
9	Dalia Zeleckienė	teisė	ne

Lietuvos bioetikos komitetas dirba vadovaudamasis Geros Klinikinės Praktikos taisyklėmis, kurias siūloma priimti Europos Sąjungos, Japonijos ir JAV valdžios struktūroms

Pirmininkas Eugenijus Gefenas

A.V.