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Title: Endothelial dysfunction and vascular maladaptation in atrial fibrillation

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Abstract:

Atrial fibrillation (AF) is the most common arrhythmia and is associated with worsened morbidity and mortality. The prevalence of AF is estimated to increase with an ageing population resulting in an ever-increasing burden on the healthcare system. Despite improvements in AF treatment, several questions remain unanswered in relation to the development and progression of AF. In this review, we discuss the evidence supporting the presence of vascular dysfunction in the development of AF, but also as a final common pathway explaining why AF constitutes a markedly increased risk of cardiovascular morbidity and mortality. Specifically, we summarise the work performed in humans related to the impact of AF on vascular structure and function, and whether measures of vascular function predict AF progression and the development of cardiovascular events. Subsequently, we discuss the potential mechanisms linking AF to the development of vascular dysfunction. Finally, we propose future perspectives of vascular health and AF, advocating a strong focus on regular exercise training as a safe and effective strategy to improve vascular function and, hence, reduce the risk for development and progression of AF and its associated risk for cardiovascular events.

Key words: atrial fibrillation; vascular health; endothelial function; pathophysiology; risk factors

1. Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia [1]. The clinical consequences of AF relate to an increased risk of mortality and morbidity from stroke, heart failure and death [2]. Even short episodes of AF are associated with atrial myocardial damage, expression of prothrombotic factors, activation of platelets and inflammatory cells, collectively contributing to a generalized prothrombotic state and, subsequently, increased risk for clinical events [3]. Several studies have examined the complex and, most likely, multi-faceted aetiology of AF, with a likely central role for inflammation [4]. The presence of a systemic inflammatory, prothrombotic state may also contribute to the higher risk for co-morbidities [5]. Interestingly, the presence of cardiovascular risk factors, but also inflammation, have previously been related to the presence of vascular dysfunction [6]. Hence, this review poses that endothelial dysfunction may contribute to both the development and progression of AF, but also represents a final common pathway explaining how AF constitutes a markedly increased risk of cardiovascular morbidity and mortality (***Fig. 1***).

In this review article, we discuss the evidence supporting a potential central role for the presence of vascular dysfunction to contribute to the development of AF and cardiovascular comorbidities. Specifically, we summarise the work related to the impact of AF on peripheral and central vascular structure and function, and whether measures of vascular function predict AF progression and development of cardiovascular events in patients with AF. Subsequently, we discuss the potential mechanisms linking AF to the development of vascular dysfunction. Importantly, vascular and endothelial function are often used interchangeably in current literature, but likely represent distinct characteristics. Measures of vascular function captures the interplay between the regulation of endothelial function and (structural) characteristics of the vasculature. For this reason, we will separately discuss measures of endothelial function (e.g. flow-mediated dilatation, intra-arterial infusion of vasoactive substances, reactive hyperaemia) and vascular structure (intima-media thickness, arterial stiffness, coronary artery calcification).

2. Endothelial dysfunction and vascular maladaptation in primary prevention of AF

2.1 Is AF related to the presence of endothelial dysfunction?

A frequently used measure of peripheral artery endothelial function relates to the flow-mediated dilation (FMD). Several studies support the notion that AF patients demonstrate an impaired FMD [7,8]. Indeed, Komatsu *et al*. found that FMD also related to AF severity, with an FMD of 6.5±3.5% in non-AF individuals, 5.4±2.6% in paroxysmal AF patients, and 4.3±2.1% in chronic AF patients [9]. A 1% drop in FMD relates to a 13% increase in cardiovascular risk [10]. The impaired FMD in AF patients may be restored following cardioversion [8], with preserved FMD after catheter ablation if sinus rhythm is maintained [11]. This suggests that the impaired endothelial dysfunction is linked to AF itself and is not simply the consequence of cardiovascular risk factors, as these have unlikely changed upon cardioversion.

Comparable to FMD findings (reflecting conduit artery endothelial function), reactive hyperaemia pulse amplitude tonometry index (RHI), a marker of microvascular endothelial function [12], is lower in paroxysmal and permanent AF compared to healthy controls without AF. Further, permanent AF was an independent predictor of lower RHI [13]. Other studies have found that pulse wave velocity (PWV) [14] and the augmentation index (AIx) [15] are correlated with AF, even in those without underlying cardiovascular disease [14]. These studies add further evidence that the presence of systemic vascular dysfunction, present in central and peripheral arteries, relates to AF *per se* rather than associated disease processes and/or cardiovascular risk factors [16].

2.2 Can measures of endothelial function predict occurrence of AF?

In a population-based study that included non-AF individuals, a higher baseline brachial artery diameter (Hazard ratio [HR]: 1.20 ; 95% confidence interval [CI]: 1.01-1.43, P=0.04), and lower FMD (HR: 0.79 ; 95% CI: 0.63-0.99, P=0.04) were both associated with increased risk of incident AF after a 7.1-year follow-up [17]. Furthermore, a previous study which enrolled 2,936 individuals free of AF (mean age 61±9.9 years; 50% women), followed individuals for a median 8.5 years [18]. Endothelial dysfunction preceded the development of AF, whereas each 2.8% increase in FMD was associated with a 16% decrease in AF incidence (HR: 0.84 ; 95% CI: 0.70-0.99, P<0.05) [18].

Studies related to measures of vascular stiffness have presented mixed findings, which may at least partially be explained by the measure of stiffness used. Studies that use pulse pressure, a surrogate index of central arterial stiffness and calculated through the difference between systolic and diastolic blood pressure, have presented consistent results. Age and hypertension are two important risk factors of incidence of AF and are both associated with increased arterial stiffness [19]. Progressive stiffness of the left ventricle leads to a decline in diastolic and systolic function, accompanied by an increase in end-diastolic pressure, which in turn, increases the left atrium diameter, as observed in hypertensive individuals [20]. This possible mechanism may represent the close relation between arterial stiffness, cardiac remodelling, and AF [20]. Interestingly, pulse pressure seems a strong predictor of future AF onset, an effect that is independent of traditional (e.g. age, blood pressure) and novel cardiovascular risk factors (e.g. 24h pulse pressure, left atrial diameter) [19]. AIx, another marker of central arterial stiffness, was also identified as an independent predictor of incident AF [17]. In contrast, measures of peripheral vascular stiffness, e.g. finger plethysmograph, was only unidirectionally (using a two-sample Mendelian randomization approach to estimate the causal effect) associated with risk of incident AF [21].

These observations suggest that measures of central arterial stiffness (e.g. AIx, central pulse pressure) present a stronger relation with AF development than peripheral arterial stiffness measures. This may fit with the aetiology of AF, that is strongly linked to atrial structural abnormalities that are more likely to be linked to central than peripheral measures of arterial stiffness (***Fig. 1***).

2.3 Is AF related to the presence of structural vascular abnormalities?

A popular ultrasound-based technique to examine vascular structure relates to the intima-media thickness (IMT) of conduit arteries, which is an early marker of atherosclerosis, and has been associated with risk of major adverse cardiovascular events. A recent meta-analysis aggregated three population-based cohort studies (25,767 individuals) and evaluated the association of carotid

artery IMT and incidence of AF [22]. Larger IMT and presence of carotid plaques, were strongly correlated with AF incidence [22]. Another study confirmed the close association between an elevated carotid IMT (>0.90 mm) and the presence of AF, suggesting that AF and systemic atherosclerosis are strongly associated [23]. Moreover, a larger carotid IMT was found in persistent/permanent AF patients compared to paroxysmal AF patients [16, 23], suggesting a potential graded association between AF severity and subclinical atherosclerosis.
Coronary artery calcium (CAC) burden is another useful marker of subclinical atherosclerosis, and examines vascular structure in more proximity to the cardiac origin of AF [24, 25]. Higher CAC-scores have been reported in AF patients [26], especially in persistent AF highlighting that the 'severity' of AF may relate to coronary structural abnormalities [27]. In addition, there is a stronger association between CAC progression and AF in young and middle-aged adults (<61 years old, HR: 3.53, 95% CI: 1.29-9.69) compared with older humans (≥61 years old, HR: 1.42, 95% CI: 0.99-2.04, Interaction-effect: P=0.04), which may be explained by a more rapid development of abnormal electrophysiology in those with CAC progression [28, 29].

2.4 Do structural vascular abnormalities predict occurrence of AF?

A number of studies have linked the presence of structural vascular abnormalities to the risk of developing AF. In 7,062 hypertensive patients without AF or cardiovascular disease, 117 (1.7%) developed AF after a median 36-month follow-up [30], higher carotid IMT was identified as an independent predictor of incident AF (HR: 1.51, 95% CI: 1.27-1.79, P<0.001), while some traditional cardiovascular risk factors (e.g. gender, duration of hypertension) did not predict AF. It is consistent with previous work reporting that higher IMT was an independent predictor of new-onset AF in formerly asymptomatic individuals [23].

In line with these findings pertaining to the carotid artery IMT, CAC scores have also been identified as an independent risk factor for future AF [28, 31]. In a multi-ethnic study including 5,612 individuals, any CAC progression (defined as a CAC score >0/year) [32] was associated with an increased risk for AF (HR=1.55, 95% CI=1.10, 2.19). In summary, there is link between structural vascular abnormalities including arteries in close proximity to the heart (i.e. CAC scores) and systemic atherosclerotic burden (i.e. carotid IMT), and the risk for incident AF.

2.5 What are the potential mechanisms explaining the presence of vascular dysfunction in AF?

Although many factors contribute to vascular dysfunction in AF including irregular stroke volume and disturbed pulsatile blood flow [33], we highlight two highly likely candidates: inflammation and oxidative stress. Inflammation and oxidative stress are major determinants of vascular (dys)function [34]. Therefore, atrial dysfunction in AF may create a pro-inflammatory state and enhance oxidative stress, which aggravates the imbalance of vascular homeostasis. Furthermore, inflammation and oxidative stress are major determinants of vascular function.

Inflammation. Inflammatory biomarkers C-reactive protein (CRP) and interleukin-6 (IL-6) are increased in patients with AF, but also strongly correlated with FMD [35], suggesting a possible link between inflammation, endothelial dysfunction and progression of AF. In support of this notion, CRP is significantly higher in persistent AF compared to paroxysmal AF [34]. Furthermore, Von Willebrand factor (vWF; a marker of endothelial dysfunction) initiates platelet adhesion upon vascular damage, leads to activation of the thrombo-inflammatory pathways stimulating thromboembolism, and has an increased expression in AF patients [36]. Circulating extracellular vesicles may also play a key role in AF pathophysiological process including inflammation, coagulation and angiogenesis [37]. Together, inflammation is strongly linked to the presence of AF. Recent evidence suggests a significant association between infection (inflammatory response) severity and AF progression and adverse events [38, 39]. Inflammation seems to be involved in atrial remodelling leading to the development of AF. Moreover, inflammation could also contribute to the maintenance of AF, making inflammation a central component in a positive feedback loop contributing to both the development and progressive worsening of AF [4].

Oxidative stress. Reactive oxygen species (ROS) accelerates the release and activation of pro-MMPs (matrix metalloproteinases) and the stimulation of pro-fibrotic cascades, which can lead to atrial structural remodelling and induce AF. Enhanced oxidative injury and deletion of mitochondrial deoxyribonucleic acid (mtDNA) in cardiac muscle can be found in patients with AF, which may further impair the bioenergetic function of mitochondria and lead to the oxidative cycle involved in the pathogenesis of atrial myopathy in AF [40]. In addition, some oxidative stress related pathophysiological changes in AF have been consistently demonstrated, such as increased NADPH and xanthine oxidase activity, upregulation of the renin-angiotensin system. Moreover, oxidative stress is involved in the development of a range of cardiovascular diseases which are associated with AF [41]. These combined effects of structure maladaptation, increased inflammation [4] and oxidative stress [42] contribute to endothelial dysfunction and subsequently an increased risk for both development and progression of AF.

In summary, related to the primary prevention of AF, studies examining the relation between AF and vascular function have provided strong evidence for the presence of endothelial dysfunction and structural maladaptation in patients with AF, especially when examining arteries that are in close proximity and/or relation with the heart. More importantly, presence of endothelial dysfunction and vascular abnormalities predict occurrence of AF, most likely through shared pathophysiological processes of inflammation process and oxidative stress. However, these two pathways are closely intertwined. Oxidative stress can promote inflammasome activation, which in turn, leads to increased production of cytokines (e.g. interleukin-1 and -6, IL-1 and IL-6) that develop arterial ectopy and fibrotic remodelling that can promote AF [43]. These observations of a link between endothelial dysfunction and occurrence of AF seem largely independent of the presence of cardiovascular risk factors. The clinical implication of this observation is that measuring vascular function and/or structure improves prediction of new-onset AF and possible reflects a target for pharmacological and non-pharmacological strategies to lower the risk of AF (***Fig. 2***).

3. Endothelial dysfunction and vascular maladaptation in secondary prevention of AF

In line with the observation for a potential role for vascular dysfunction to contribute to the development of AF [11], vascular dysfunction may also predict cardiovascular co-morbidities in subjects with AF. Of note, AF seems associated with development of a high number of cardiovascular risk factors, which may exacerbate endothelial dysfunction [44]. In addition, AF leads to hemodynamic changes that may also aggravate endothelial dysfunction, further contributing to the development of cardiovascular events [45, 46].

3.1 Does endothelial dysfunction predict AF recurrence?

Several studies have examined whether endothelial dysfunction relates to poor outcomes in AF. For example, measures of impaired endothelial function in macrovessel (i.e. lower FMD) [11] or in microvessels (i.e. lower RHI) [47, 48] at baseline appears to be an independent predictor for arrhythmia recurrence following catheter ablation. Similar findings have been observed when examining arterial stiffness, for example, AF patients within the highest quartile of arterial stiffness having a 1.6-fold higher AF recurrence rate compared to those in the lowest quartile [49]. To support this concept, higher AIx has been linked to the recurrence of AF [50] and the development of paroxysmal AF [51], perhaps related to left ventricular hypertrophy [17].

These observations are consistent with endothelial dysfunction independently predicting incident AF, suggesting that endothelial dysfunction represents an integrated pathway in the development and progression of AF. Despite the strong evidence for a relationship between vascular dysfunction and AF recurrence, no studies have explored whether structural vascular characteristics are related to AF recurrence.

3.2 Does endothelial dysfunction predict AF-related cardiovascular events?

Despite the overwhelming evidence that measures of endothelial function independently predict cardiovascular disease [52, 53] and adverse events [54] in individuals with established and pre-clinical cardiovascular disease, few studies have explored whether measures of endothelial function relate to cardiovascular events in AF patients. For example, impaired endothelial function measured using the FMD is an independent and significant predictor of cardiovascular events in AF patients [55, 56]. In AF patients, arterial stiffness, assessed using the peripheral PWV, is considered as an independent predictor of cardiovascular events and improve the prediction of adverse cardiovascular events when it is added to the standard clinical, biochemical, and echocardiographic parameters [57].

In a meta-analysis including 5,648 individuals free of AF with a follow-up of 45 months, AIx was determined as an independent predictor of future incident of cardiovascular and all-cause mortality, independent from peripheral pressure and heart rate measures [58]. Higher AIx has also been significantly correlated with AF-specific cardiac remodelling such as left atrial enlargement [51], which could lead ultimately to cardiovascular events such as stroke and atrial thrombosis.

3.3 Do structural vascular adaptations predict cardiovascular events?

Carotid IMT has been shown to be associated with both coronary and cerebral vascular events in several AF studies [59-61]. For example, abnormal IMT and presence of carotid plaque in the ARIC study significantly increased the risk of stroke, and marginally increased the clinical risk prediction of stroke in combination with the CHA_2DS_2-VASc score [61]. AF patients with carotid plaque have significantly increased risk of cardio- and cerebrovascular adverse outcomes [62], and complex aortic plaque is an independent predictor of ischaemic stroke in patients with AF [63]. Indeed, patients with both AF and aortic atherosclerotic plaque ≥4.0mm demonstrated worse atherosclerosis burden and predicted long-term cardiovascular events, including stroke [64]. It is also consistent with the work related to carotid and aorta atherosclerotic burden, where CAC scores independently predict coronary artery disease [65], stroke [66], and future cardiovascular events in AF patients [24, 25]. Patients with persistent AF have a significantly higher prevalence of subclinical coronary artery disease (due to a higher coronary artery disease-burden [CAC score]) when compared to paroxysmal AF patients [27].

In summary, studies provide compelling support that presence of vascular dysfunction and/or structural vascular maladaptation (inward remodelling) is frequently present in AF. Furthermore, vascular dysfunction seems to predict AF recurrence following ablation therapy, whilst vascular dysfunction and structural maladaptation are both independently related to the occurrence of adverse cardiovascular events in these patients. Therefore, these studies therefore support an important role for vascular dysfunction in mediating AF-related morbidity and mortality, and provide a rationale for measuring vascular function and structural maladaptation in AF patients to improve risk stratification and targeted therapy.

3.4 Mechanisms explaining the association between vascular dysfunction and AF-related cardiovascular events.

The presence of traditional cardiovascular risk factors in patients with AF represent one factor contributing to the development and progression of endothelial dysfunction and vascular maladaptation, both contributing to an increased risk for AF-related cardiovascular disease and events. In addition, other pathways may contribute to these vascular adaptations (***Fig. 3***).

From a mechanistic point of view, the loss of organised atrial contraction associated with AF may lead to a beat-to-beat haemodynamic variations [13]. These irregular patterns in flow and pressure reduces maximal blood flow and atrial perfusion dysregulation, leading to a detrimental effect on atrial blood supply [67, 68]. The latter also includes a reduction of capillary density, imbalanced myocardial oxygen supply-demand ratio, and coronary perfusion impairment [69], all resulting in impaired microvascular function in the coronary arteries [70]. The irregular haemodynamic changes also lead to an irregular pulse wave, blood flow and shear stress pattern through central (and to a lesser extent, peripheral) arteries [33]. These shear stress patterns, characterised by increased retrograde flow and bidirectional flow, results from the irregular blood flow velocity [71-73]. Consequently, AF is associated with a marked decrease in eNOS expression and NO bioavailability [74], and higher levels of the vasoconstrictor endothelin-1 [75, 76], all of which exacerbate endothelial dysfunction [77] and plaque formation [78]. These abnormal patterns seem to especially affect central arteries, possibly contributing to the observation that central measures of vascular function and structure may have stronger prognostic value for AF-related events compared to more peripheral measures. However, this hypothesis requires further exploration (***Fig. 3***).

4. Exercise and AF

Emerging evidence demonstrates a variety of benefits of increased physical activity levels for patients with AF. Specifically, one fourth of new cases of AF in older adults may be attributable to absence of moderate leisure-time activity and regular walking [79]. A recent systematic review of 4 interventional studies (498 participants) found a positive effect of lifestyle and risk factor management interventions significantly decreased AF episode severity, AF frequency, and AF duration [80].

One randomised controlled trial demonstrated that weight reduction with intensive risk factor management (e.g. goals for regular exercise, lipid management, glycaemic control, and blood pressure reduction) was associated with beneficial cardiac remodelling and reduced AF burden and severity in overweight or obese patients [81, 82]. Indeed, regular exercise in patients with AF has been associated with lower risk of all-cause mortality and thromboembolic events irrespective of gender, age, or risk of stroke[83] and improved sinus rhythm maintenance [84]. In addition, for every 1 MET increase in cardiorespiratory fitness via exercise training, AF recurrence is reduced by 9% [82, 85].

These studies highlight the potency of regular physical activity as an additive therapy in the management of AF, both related to the primary and secondary prevention of AF [86, 87]. Nonetheless, important questions remain unanswered. First, a key question relates to the optimal dose, type and frequency of exercise training to optimally benefit from exercise training. Related to this topic, little work has focused on the optimal timing of exercise prior to and/or after cardioversion in AF. Finally, little work has focused on the potential underlying mechanisms explaining the cardioprotective effects of regular physical activity for AF, which may relate to the direct effect on cardiac remodelling and health, but also on circulating factors and/or improvement in vascular function and structure. Better understanding of these mechanisms will contribute to optimal prescription of exercise as medicine for AF.

5. Future perspectives for vascular function and AF

Although the pathogenesis of AF is complex and most likely multifaceted, the work summarised in this review strongly supports a central role for endothelial dysfunction and structural vascular abnormalities to contribute, as a potential final common pathway, to the development and progression of AF. Another observation from this review is that AF is related to vascular dysfunction and structural vascular abnormalities that is closely linked to AF recurrence and development of cardiovascular events.

The evidence is suggestive of a potential causative role for endothelial dysfunction and vascular remodelling for AF occurrence, recurrence and AF-related complications, but firmly establishing causation would require large prospective studies, supported by randomised trials. Nonetheless, such vascular abnormalities could also reflect common risk factors, including ageing, hypertension, diabetes etc – and the dynamic nature of risk factors changing with ageing and incident comorbidities [88-90]. The full evaluation is part of the overall characterisation of AF, the 4S-AF scheme: Stroke risk, Symptom severity, Severity of arrhythmia burden and Substrate [91]. The latter clearly includes evaluation of comorbidities and structural heart disease, as recommended by guidelines [92].

A potential clinical consequence is that measures of vascular function and structure may improve on existing assessments and risk stratification of new onset and recurrence of AF. This could lead to improved and personalised risk prediction in patients with AF. Another potential clinical consequence of these observations is that presence of systemically present endothelial dysfunction and structural maladaptation may be an important target in the primary and secondary prevention of AF, but also in minimising risks for AF-related cardiovascular disease and/or events. Whilst pharmaceutical strategies could specifically target endothelial function in AF patients, one other highly relevant strategy may relate to adopting regular exercise training [93]. It seems especially relevant given the well-established effect of regular exercise on improving vascular function and structure [93-95], but also on improving the risk factors management in addition to the regular care such as appropriate anticoagulation and rate and rhythm control [96, 97]. Indeed, regular exercise in patients with AF has been associated with lower risk of all-cause mortality and thromboembolic events [83], but also improved sinus rhythm maintenance [84]. At the very least, a stronger focus on endothelial function in AF patients likely enhances clinical management of AF as it improves prediction of AF, AF recurrence, and AF-related cardiovascular events, but also represents a sensible target in the treatment of AF.

6. Conclusion and clinical perspective

Cardiovascular diseases are a major cause of global mortality [98], accounting for approximately 31% of all deaths [99]. Endothelial dysfunction is one of the major determinants of atherosclerosis [100, 101], significantly associated with higher thrombotic events [102] and cardiovascular mortality [103]. So far, a number of techniques have been developed to assess endothelial function, which provide reliable references for the diagnosis and prognosis of vascular disease [104]. Evidence confirm that some risk factors such as obesity [105], age [106], hypertension[107], and physical inactivity [108-110] can exacerbate endothelial dysfunction. These lines of evidence strongly support future studies to pay more attention to the evaluation and maintenance of vascular endothelial function in patients with AF. These recommendations are on top of improvements of vascular disease risk, but also lifestyle modification [111].

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Conflict of interest

The authors declare that there is no conflict of interest

Authors' contributions

S.Q. and D.T. contributed to the conception or design of the work. S.Q. contributed to writing the original draft, reviewing and editing. M.B. and B.B. contributed to writing the original draft and reviewing. G.L. and D.T. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Figure Legends

Fig.1 The association among endothelial dysfunction, AF and cardiovascular events

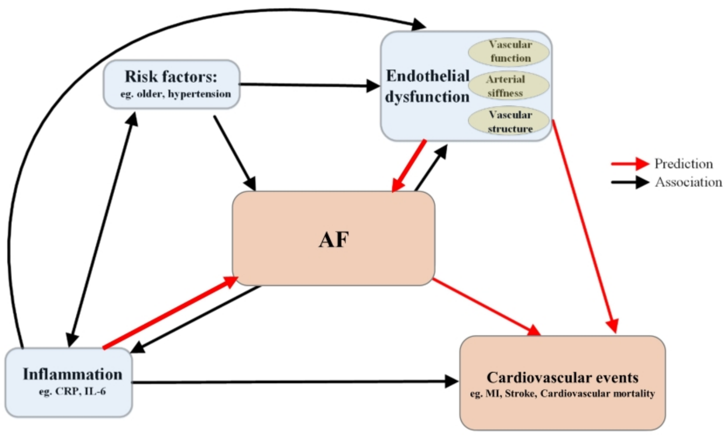
AF: atrial fibrillation, CRP: c-reactive protein, IL-6: interleukin 6, vWF: von willebrand factor, MI: myocardial infarction

Fig.2 The key role of endothelial function in the primary prevention of AF

AF: atrial fibrillation, CRP: c-Reactive Protein, IL-6: interleukin-6, eNOS: endothelial nitric oxide synthase, NO: nitric oxide, ROS: reactive oxygen species, Pro-MMPs: matrix metalloproteinases, vWF: von Willebrand factor

Fig.3 The key role of endothelial function in secondary prevention of AF

AF: Atrial fibrillation; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide



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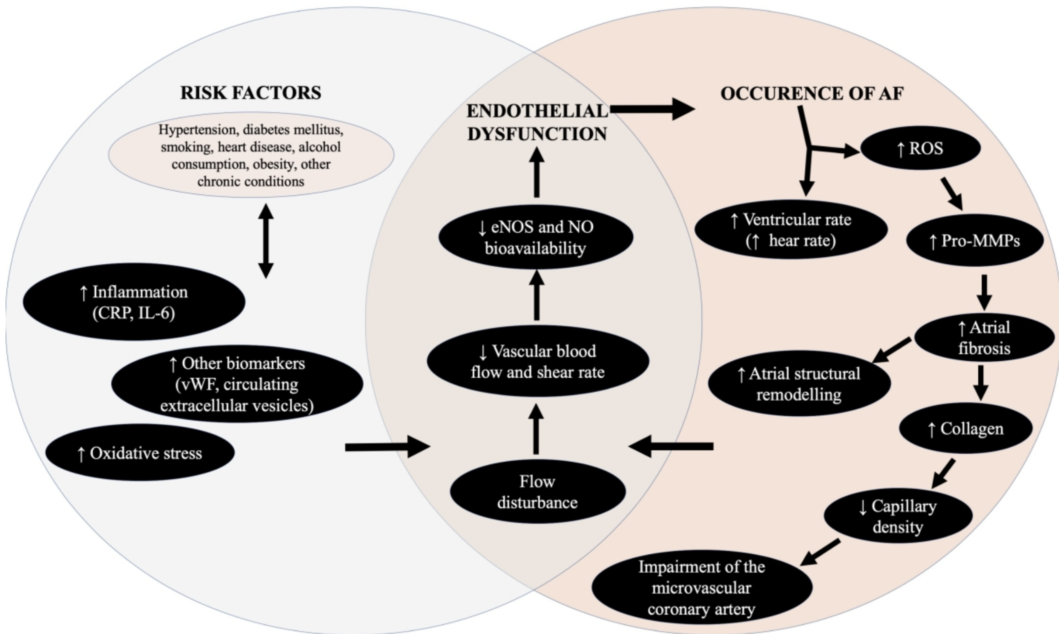

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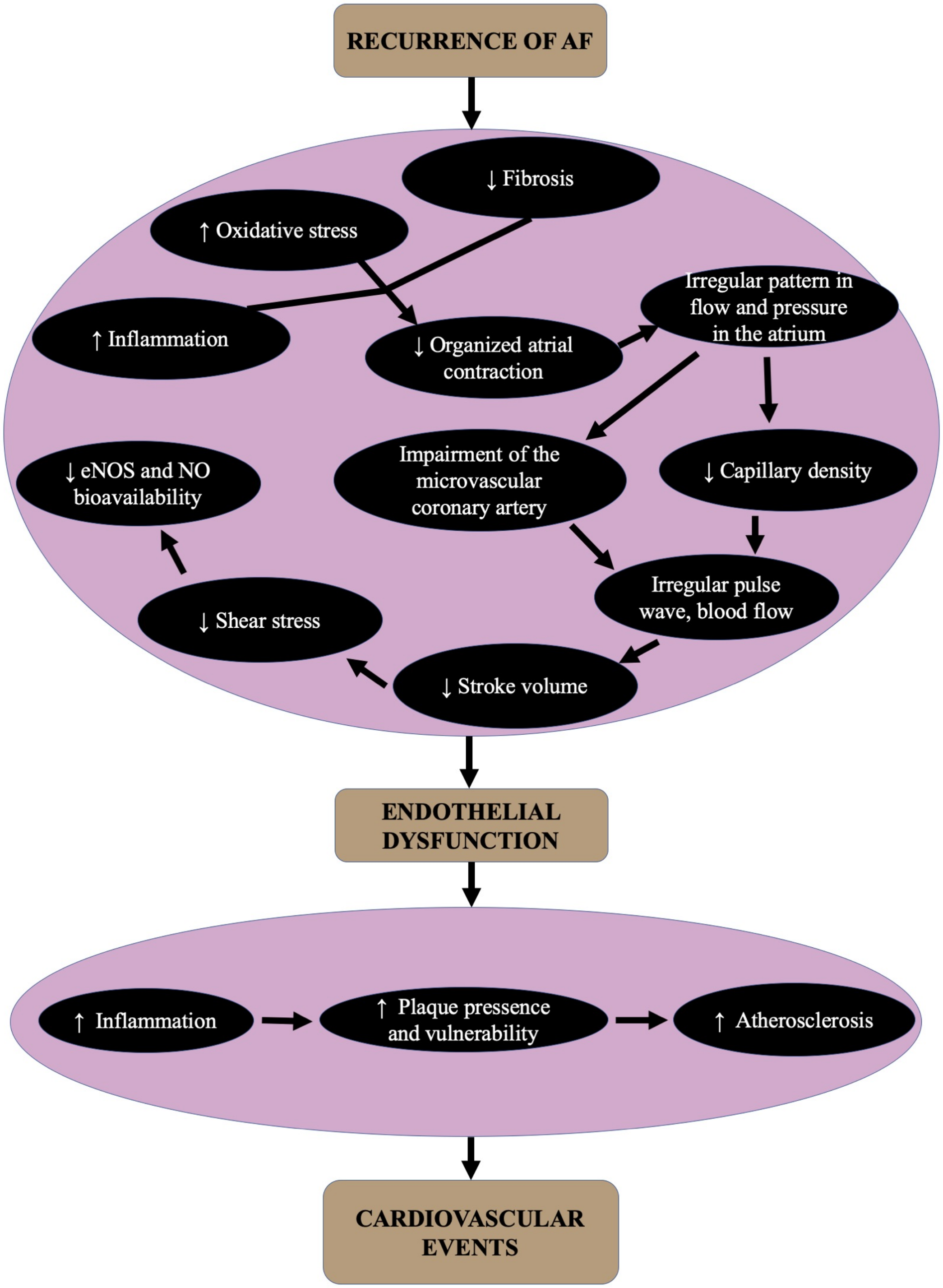

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