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REVIEW ARTICLE

Endothelial function in patients with atrial fibrillation

Ahsan A. Khan[a] [iD], Graham N. Thomas[a] [iD], Gregory Y. H. Lip[b,c] [iD] and Alena Shantsila[b]

[a]College of Medical and Dental Sciences, Institute of Applied Health Research, University of Birmingham, Birmingham, UK; [b]Faculty of Health and Life Sciences, Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, UK; [c]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark

ABSTRACT

Atrial fibrillation (AF) is the most common heart arrhythmia and is associated with poor outcomes. The adverse effects of AF are mediated through multiple pathways, including endothelial dysfunction, as measured by flow-mediated dilatation. Flow-mediated dilatation has demonstrated endothelial dysfunction in several conditions and is associated with poor outcomes including mortality, yet can be improved with medical therapy. It is thus a useful tool in assessing endothelial function in patients. Endothelial dysfunction is present in patients with AF and is associated with poor outcomes. These patients are generally older and have other co-morbidities such as hypertension, hypercholesterolaemia and diabetes. The precise process by which AF is affiliated with endothelial damage/dysfunction remains elusive. This review explores the endothelial structure, its physiology and how it is affected in patients with AF. It also assesses the utility of flow mediated dilatation as a technique to assess endothelial function in patients with AF.

KEY MESSAGES

- Endothelial function is affected in patients with atrial fibrillation as with other cardiovascular conditions.
- Endothelial dysfunction is associated with poor outcomes such as stroke, myocardial infarction and death, yet is a reversible condition.
- Flow-mediated dilatation is a reliable tool to assess endothelial function in patients with atrial fibrillation.
- Patients with atrial fibrillation should be considered for endothelial function assessment and attempts made to reverse this condition.

Introduction

Atrial fibrillation (AF), as the most common cardiac dysrhythmia is associated with poor outcomes, including stroke [1]. The incidence of stroke attributable to AF increases from 1.5% at age 50–59 years to 23.5% at age 80–89 years [2]. Approximately, 15 million people worldwide have a stroke each year, of which at least 15% have been directly attributed to clinically diagnosed AF [1,3]. Compared to people without AF, people with AF have distinctly reduced survival rates, with risk factor-adjusted odds ratio for death of 1.5 in men and 1.9 in women [4]. The adverse effects of AF are perceived to be due to haemodynamic changes with multiple factors leading to a prothrombotic state *in vivo* [5]. These include abnormal haemostasis including inappropriate platelet activation, intra-atrial blood stasis, structural heart disease and endothelial dysfunction/damage causing predisposition to thrombogensis [5]. In short, the commonly known Virchow's triad of factors, hypercoagulability, flow disturbance and endothelial dysfunction, which are necessary for the development of thrombosis are all present in patients with AF.

The precise process by which AF is affiliated with endothelial damage/dysfunction remains elusive, given that indices of endothelial dysfunction such as von Willebrand factor (vWF) are abnormal even in lone AF [6]. Flow abnormalities may occur in AF due to heart failure (a commonly associated condition), valvular heart disease or the irregularity of the heart rate itself. This results in turbulent flow both in the left atrium and systemically. Loss of shear stress, as occurs in conditions of turbulent flow is related to reduced expression of endothelial nitric oxide (NO) synthase (eNOS),

CONTACT Alena Shantsila ✉ s.shantsila@liverpool.ac.uk 🖵 Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, 6 West Derby Street, Liverpool, L7 8TX, UK

a key regulator of endothelial function. This review will explore the endothelial structure, its physiology, the role of NO and how endothelial function is affected in patients with AF.

Endothelial structure

Endothelium refers to cells that line the interior surface of blood vessels, forming an interface between circulating blood in the lumen and the vessel wall. It is a single layer of simple squamous cells lining the entire circulatory system, from the heart to the smallest capillaries [7]. Endothelium is mesodermal in origin. In a straight section of a blood vessel, vascular endothelial cells typically align and extend in the direction of fluid flow. Endothelial cells are able to alter their structure and phenotype depending on the vessel type. For example, endothelial cells lining the artery tend to be thicker than those in capillaries, which are fenestrated and thinner to allow for exchange of gases, nutrients and metabolites. Furthermore, endothelial cells can respond differently to stimulation in different vascular beds and even in different sections of the same vascular bed [8–10].

Endothelial physiology

The endothelium is considered a dynamic organ [7]. It constitutes several unique functions in vascular biology by responding to various hormones, neurotransmitters, vasoactive factors and processes which then affect blood vessel tone (vasomotion) and haemostasis (thrombosis, platelet aggregation and inflammation) [7]. The endothelium releases several vasoactive factors, which are either vasodilatory such as NO, prostacyclin (PGI_2) and endothelium-derived hyperpolarizing factor (EDHF) or vasoconstrictive factors such as thromboxane (TXA_2) and endothelin-1 (ET-1) [11]. The balanced production of these vasoactive factors is atheroprotective, whereas disrupted production of these factors leads to endothelial dysfunction. Endothelial dysfunction is a hallmark of vascular diseases and has been shown to predict future adverse cardiovascular events such as cardiac death, myocardial infarction, unstable angina and stroke. It is also present in inflammatory disease processes, such as rheumatoid arthritis or systemic lupus erythematosus (Figure 1) [12]. Endothelial dysfunction presents a final common pathway or "barometer" of the combined impact of traditional atherosclerotic risk factors; thus assessment of endothelial dysfunction in humans presents an attractive option for determination of risk

associated with thrombogenesis and combined risk factor impact on atherogenesis [13].

Nitric oxide

Nitric oxide (NO) has been recognized as a key component in regulation of vascular tone and in mediating the prothrombotic state in AF. It is synthesized by NO synthase (NOS) enzyme, which converts amino acid L-arginine to NO [14]. Three isoforms of NOS exist, including neuronal isoform (nNOS), which produces NO that act as a neuronal messenger in the synapses; inducible isoform (iNOS), expressed in cells exposed to inflammatory mediators or injurious stimulus and; endothelial NOS (eNOS), which produces NO in the vasculature [15–17]. The property of blood vessel to dilate is heavily dependent on the activity of eNOS [11].

Inactive eNOS is bound to a protein called caveolin and is situated in small openings within the cell membrane called caveolae (Figure 2) [18]. eNOS detaches from caveolin and is activated when intracellular levels of calcium increase [18]. The detachment of eNOS can be influenced by NO agonists such as bradykinin (BK), acetylcholine (ACh), adenosine tri-phosphate (ATP), adenosine di-phosphate (ADP), substance P and thrombin by releasing calcium from the endoplasmic reticulum [19,20]. Once intracellular calcium stores are depleted, a signal is sent to the membrane receptors to open calcium channels allowing extracellular calcium release into the cell [21,22]. Calcium attaches to cytoplasmic calmodulin, and undergoes structural changes which allow it to bind to eNOS [23]. eNOS then converts L-arginine into NO [14].

Once synthesised, NO diffuses across the endothelial cells into the adjacent smooth muscle, where it binds to the soluble guanylyl cyclase (sGC) enzyme [24]. The activated sGC enzyme escalates the conversion rate of guanosine triphosphate (GTP) to cGMP, which decreases smooth muscle tension of blood vessels [25]. Furthermore, cGMP reduces calcium release from the sarcoplasmic reticulum in the smooth muscle cell [26]. Both actions lead to relaxation of smooth muscle cells as shown in Figure 2. These processes are continuously active in producing NO to maintain basal vasodilator tone.

Endothelial function in AF

It has been established that eNOS expression is regulated by a variety of stimuli [27,28]. One of the key physiologically important stimuli is laminar shear
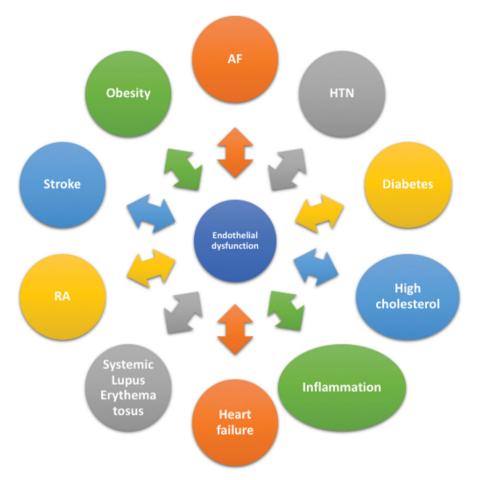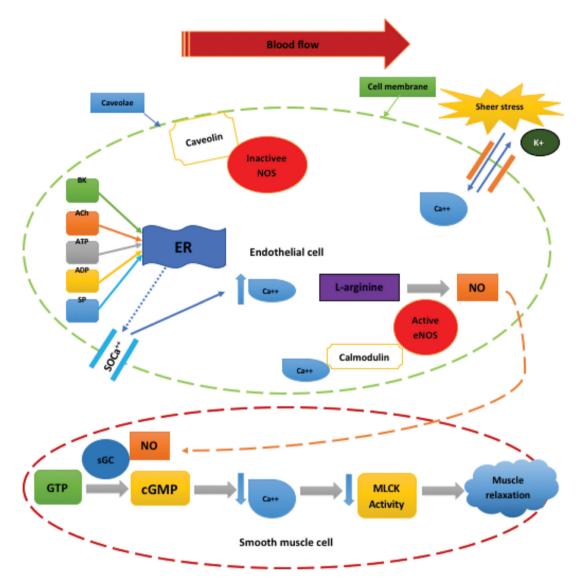
Figure 1. Endothelial dysfunction as a link to several conditions. AF: atrial fibrillation; HTN: hypertension; RA: rheumatoid arthritis.

stress, the tangential force exerted by flow over the surface of the endothelium. Areas of the vascular system exposed to high shear are protected from the development of atherosclerosis, while areas exposed to low shear are prone to atherosclerotic lesion development [29]. It is thought that increases in eNOS caused by shear may contribute to this phenomenon as NO has antithrombotic properties as described earlier. Thus a healthy vessel has good concentration of eNOS.

Shear stress results from increased blood flow in the vessel. Flow-mediated shear stress regulates the expression of NOS, and is therefore, down-regulated at sites with low flow velocity [30–32]. Since AF leads to a loss of organised atrial contraction and predisposes to low blood flow in the left atrium, AF is associated with a marked decrease in eNOS expression and NO bioavailability [33]. Reduced NO bioavailability and resulting endothelial function impairment may explain AF as a cause of endothelial dysfunction. In an animal model, laminar blood flow in sinus rhythm and the cyclic stretch of atrial endocardial cells acted as a

stimulus to maintain normal endocardial expression and function of NOS [33].

NO has displayed strong antithrombotic effects when released from activated platelets in the arterial endothelium [34]. It prevents platelet recruitment to the developing thrombus, while also impeding PAI-1 activity [35]. An animal model of AF has shown reduced NO bioavailability and an increase in PAI-1 expression due to diminished expression of NOS in the left atrium. This is possibly as a result of impaired atrial contraction and a subsequent decrease in shear stress [33]. The concentrations of NO are also reduced in the left atrial appendage (LAA) compared with control animals, providing further evidence to the concept that atrial thrombus is a common occurrence in the LAA [33]. Although it is important to bear in mind that the method of induction of AF in this animal model was significantly different compared to development of AF seen in humans. The delay between the onset of AF and hypercoagulability as discussed earlier is consistent with the observation that AF induces endocardial dysfunction, since downregulation of NOS

Figure 2. Endothelial nitric oxide production and its action on vascular smooth muscle cell. Ach: acetylcholine; BK: bradykinin; ATP: adenosine triphosphate; ADP: adenosine diphosphate; SP: substance P; $SOCa^{2+}$: store-operated Ca channel; ER: endoplasmic reticulum; NO: nitric oxide; eNOS: endothelial nitric oxide synthase; GTP: guanosine 5′-triphosphate; sGC: soluble guanylyl cyclase; cGMP: cyclic guanosine-3′, 5-monophosphate; MLCK: myosin light chain kinase. *When Ca^{2+} stores of the endoplasmic reticulum are depleted, a signal is sent to $SOCa^{2+}$ channel which allows extracellular Ca^{2+} into the endothelial cell.

and its subsequent effects take time to develop [33]. Additionally, patients with AF are generally older and have other co-morbidities such as hypertension, hypercholesterolaemia and diabetes, all of which exert adverse effects on the endothelial function.

Mechanical stimuli have been shown to influence various aspects of endothelial function [33]. The mechanisms linking mechanical forces to gene expression remain poorly defined [30]. Shear stress is known to activate numerous intracellular signalling molecules, including tyrosine kinases (in particular c-Src), G-proteins, PI-3 kinase, c-Jun N-terminal kinase (JNK), protein kinase C and mitogen activated protein kinases

(MAPK) extracellular-related kinases [36,37]. There is further evidence that shear stress may enhance the activity of the eNOS protein promoter through transcriptional regulation of the eNOS gene [38]. The commonly accepted theory is that constant shear stress produced by unidirectional flow maintains normal eNOS expression by activation of the tyrosine kinase c-Src, which then leads to deviating pathways modulating both eNOS transcription rate and also its messenger RNA (mRNA) stability [30]. Shear stress also acutely increases NO bioavailability in the endothelium by stimulating eNOS phosphorylation [39,40]. The constitutive eNOS importantly regulates vascular

haemostasis [31]. This allows the endothelium to respond to the stress and dilate accordingly to compensate for increase in blood flow.

In addition to shear stress causing endothelial dysfunction in AF, there are other mechanisms linking AF with endothelial dysfunction. Dimethylarginines, including asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) are thought to play a part in the endothelial dysfunction seen in AF. ADMA and SDMA are both endogenous methylated analogues of L-arginine, the precursor of NO. Elevated levels of ADMA inhibit NO synthase, thus leading to endothelial dysfunction, oxidative stress and inflammation in cardiovascular diseases [41,42]. SDMA does not inhibit NOS directly but interferes with the cellular uptake of L-arginine [43]. Elevated levels of ADMA and SDMA have been found in patients with AF and this may point towards another mechanism of endothelial dysfunction seen in patients with AF [44–47].

Furthermore, AF induces atrial inflammation and elevation of c-reactive protein and cytokines, exerting a proinflammatory effect on endothelial cells which can potentially lead to endothelial dysfunction [48]. The Renin–Angiotensin system (RAS) may also play a part in endothelial dysfunction seen in patient with AF. Angiotensin II increases atrial cell death leading to AF. Moreover, RAS contributes to the myocardial and vascular oxidative stress in AF [48]. This is in addition to RAS effect on increasing blood pressure and leading to endothelial dysfunction.

Several studies have shown that endothelial dysfunction in terms of reduced NO activity is one of the earliest markers in patients with atherogenic risk factors [7,49–51]. Endothelial dysfunction, as demonstrated by endothelial-dependent flow-mediated dilatation (FMD) has also been shown to be present in AF [52–57]. Plasma von Willebrand factor (vWF), a marker of endothelial damage/dysfunction is consistently elevated in AF and has been associated with adverse outcomes [58]. Multiple studies have shown that restoration of sinus rhythm in patients with AF leads to improvement of endothelial function [59,60]. Thus, further providing evidence that AF is perhaps a cause of endothelial dysfunction and that endothelial dysfunction is a reversible condition.

Role of flow-mediated dilatation (FMD) in assessing vascular function

Assessment of endothelial function is a good predictor of future cardiac events in groups at risk of cardiovascular disease or those with established cardiovascular disease [61,62]. Such assessment at an individual level (unlike group level) is in fact poor in predicting outcomes. Nevertheless, endothelial dysfunction is common in individuals with cardiovascular risk factors [63–65]. Changes in NO have been quantified by measurement of nitrate/nitrite product in the plasma (NOx), but also indirectly by the validated non-invasive technique of FMD [66–68]. This technique measures a vasodilatory response attributed to endothelial NO production in response to situations of elevated shear stress [69,70]. Reduced vasodilatory response following an increase in shear forces is representative of impaired NO bioavailability [71]. Thus, FMD is a good surrogate marker of NO bioavailability.

FMD has been widely used to demonstrate endothelial dysfunction in both cardiovascular disease and its risk factors (Table 1) [74–76,82,83,86,94,96]. FMD provides independent prognostic information that may exceed that available from traditional risk factors measurement based on the concept of direct assessment of the function of the vascular system [13]. Several studies have shown that endothelial function can be improved by treatment of cardiovascular disease or its risk factors [7,77,78,97]. Indeed, FMD has been established as a reliable and reproducible technique for assessment of endothelial dysfunction [96,98].

The FMD technique has a widely accepted standardised protocol, which allows accurate comparison between heterogenous groups and serially over time [96]. Due to accessibility and characteristics of the vessel, brachial artery is typically used for this technique. FMD protocol involves a baseline period of 1–2 min of scanning of the brachial artery followed by a 5-min period of cuff inflation on the study forearm (distal to brachial artery) to induce tissue ischaemia and dilatation of downstream resistance vessels via autoregulatory mechanisms. The cuff placement close to the wrist is dependent on NO, while on the upper arm is only partially mediated by NO [13,70]. Furthermore, upper arm cuff placement leads to initiation of local ischaemia due to complete blood flow occlusion. Five minutes of limb occlusion is adequate to evoke endothelium-dependent dilatation, as longer cuff durations have shown a non-NO response [99]. Upon cuff release, an expected sudden increase in blood flow (reactive hyperaemia) through the artery fills the dilated vessels and in doing so exerts shear stress on the endothelial cells [96]. The resulting dilatation, which usually peaks at 60–90 s post-cuff release is dependent on NO activity [69].

Table 1. Use of FMD in cardiovascular and associated risk factor conditions.

Author(s)	Year	Condition studied	Number of patients	Summary
Anderson et al. [72]	1995	Coronary artery disease (CAD)	50	Patients with CAD had worse FMD than those with normal coronary arteries ($4.5 \pm 4.6\%$ versus $9.7 \pm 8.1\%$, $p<.02$)
Anderson et al. [73]	2000	CAD	80	Quinapril associated with significant improvement in FMD ($1.8 \pm 1\%$, $p<.02$). No change observed with Losartan ($0.8 \pm 1.1\%$, $p=.57$), Amlodipine ($0.3 \pm 0.9\%$, $p=.97$) or Enalapril ($-0.2 \pm 0.8\%$, $p = .84$)
Borschel et al. [53]	2019	Atrial fibrillation (AF)	466 AF versus 14,330 non-AF	Decreased FMD in patients with AF observed but this was not statistically significant
Celermajer et al. [68]	1992	Atherosclerosis [Smoking, familial hypercholesterolaemia (FH), CAD]	50 controls versus 20 cigarette smokers versus 10 FH children versus 20 CAD	FMD was reduced or absent in smokers (4%), FH children (0%) and adults with CAD (0%) when compared with controls (11%) ($p<.001$)
Celermajer et al. [74]	1993	Atherosclerosis (smoking)	80 controls versus 80 current smokers versus 40 ex-smokers	FMD was impaired or absent in smokers compared to controls ($4 \pm 3.9\%$ versus $10 \pm 3.3\%$, $p<.0001$). FMD was inversely related to lifetime dose smoked
Chambers et al. [75]	1999	Hyperhomocysteinemia	17	Inverse linear relationship between homocysteine concentration and FMD ($p<.001$)
Clarkson et al. [76]	1997	Family history of CAD	50 first-degree relatives versus 50 controls	FMD was impaired in family history group compared to control group ($4.9 \pm 4.6\%$ versus $8.3 \pm 3.5\%$, $p<.005$)
Dupuis et al. [77]	1999	CAD, Hypercholesterolaemia	30 (Pravastatin) versus 30 (placebo)	FMD increased with Pravastatin ($4.93 \pm 0.81\%$ to $7.0 \pm 0.79\%$, $p=.02$). FMD was unchanged with placebo ($5.43 \pm 0.74\%$ to $5.84 \pm 0.81\%$)
Felmeden et al. [78]	2003	Hypertension (HTN)	76 HTN versus 48 controls	FMD lower in HTN patients compared with control ($4.8 \pm 1.3\%$ versus $8.6 \pm 2.2\%$, $p<.001$). After intensified hypertensive treatment, FMD improved ($4.8 \pm 1.3\%$ (baseline) to $7.3 \pm 1.7\%$, $p<.001$)
Freestone et al. [52]	2008	AF	40 AF versus 26 NSR	Worse FMD in AF patients than NSR patients (0.0 versus 8.9%, $p<.0001$)
Gerhard et al. [79]	1998	Post menopause, hypercholesterolaemia	17	Oestradiol therapy improved FMD compared with placebo ($11.1 \pm 1.0\%$ versus $4.7 \pm 0.6\%$, $p<.001$). Modest decrease in total and LDL cholesterol with oestradiol
Gokce et al. [80]	2002	CAD	187	45 patients with cardiovascular event. FMD independent predictor of events ($4.9 \pm 3.1\%$ versus $7.3 \pm 5\%$; $p<.001$)
Gokce et al. [61]	2003	Peripheral arterial disease (PAD)	199	Worse FMD in patients ending up having a cardiovascular event (cardiac death, myocardial infarction, unstable angina, stroke) ($4.4 \pm 2.8\%$ versus $7.0 \pm 4.9\%$, $p<.0001$)
Hornig et al. [81]	1998	Heart failure	30	Quinaprilat improved FMD by 40% ($10.2 \pm 0.6\%$ versus $6.9 \pm 0.6\%$; $p<.01$) whereas enalaprilat had no effect
Iiyama et al. [82]	1996	Hypertension	13 HTN versus 13 controls	FMD found to be less in patients with HTN than controls ($13.1 \pm 1.6\%$ versus $18.5 \pm 1.9\%$, $p<.05$)
Komatsu et al. [54]	2018	AF	184 paroxysmal AF (PAF) versus 53 chronic AF versus 79 sinus rhythm controls	FMD was $5.4 \pm 2.6\%$ in PAF patients versus $4.3 \pm 2.1\%$ in chronic AF versus $6.5 \pm 3.5\%$ in controls, which was significant (all, $p<.05$)
Lekakis et al. [83]	1997	Diabetes mellitus	26 insulin-dependent diabetes mellitus (IDDM) without microalbuminuria versus 5 IDDM with microalbuminuria versus 26 controls	FMD was lower in patients with IDDM with and without microalbuminuria compared with controls ($0.75 \pm 2.5\%$ versus $5.8 \pm 7\%$ versus $11 \pm 7\%$, $p=.003$ and .01, respectively)
Lieberman et al. [84]	1994	Post menopause	13	FMD greater in patients receiving Oestradiol than placebo (13.5 versus 6.8%, $p<.05$)
Mazaris et al. [55]	2014	AF	35 PAF versus 117 permanent AF	Patients with permanent AF had impaired FMD compared to PAF ($4.09 \pm 1.67\%$ versus $6.83 \pm 1.38\%$, $p<.001$). Endothelial dysfunction associated with atrial remodelling in patients with AF and implicated in the progression from paroxysmal to permanent AF

Table 1. Continued.

Author(s)	Year	Condition studied	Number of patients	Summary
Modena et al. [85]	2002	Hypertension	400	47 patients with cardiovascular event. Majority of these had poor FMD response ($7.1 \pm 2.5\%$ versus $13.9 \pm 2.6\%$). FMD can be improved following 6 months of antihypertensive treatment
Neunteufl et al. [86]	1997	CAD	44 (CAD) versus 30 (angina pectoris – non CAD) versus 14 controls	CAD patients showed markedly impaired FMD compared to non-CAD group and to control ($5.7 \pm 4.8\%$ versus $12.6 \pm 6.7\%$ versus $15.7 \pm 3.9\%$, $p<.00001$)
Neunteufl et al. [87]	2000	CAD	73	27 patients with cardiovascular event. FMD $<$ 10% predictive of events
O'Neal et al. [88]	2014	AF	2936	Smaller brachial FMD values associated with higher rates of AF. Each 1SD increase in %FMD values (SD, 2.8%) associated with less incident AF (hazard ratio 0.84; 95% CI 0.70–0.99)
Perri et al. [89]	2015	AF	514	Patients who experienced a cardiovascular event showed significantly reduced FMD compared to those who did not (3.06% [IQR 0.00–6.00] versus 4.67% [IQR 1.58–8.22], $p=.027$)
Polovina et al. [56]	2013	AF	38 AF versus 28 controls	Median FMD significantly lower in AF patients compared to control (5.0% [IQR 2.87–7.50%] versus 8.85% [IQR 5.80–12.50%], $p<.001$)
Rossi et al. [62]	2008	Post menopause	2264	FMD $\leq 4.5\%$ associated with a greater cardiovascular event rate compared with FMD $> 4.5\%$
Schachinger et al. [90]	2000	CAD	147	28 patients with cardiovascular event. FMD independent predictor of events
Shaikh et al. [91]	2016	AF	3921	Lower FMD associated with an increased risk of incident AF (hazard ratio: 0.79, 95% CI 0.63–0.99, $p=.04$)
Shaposhnikova et al. [92]	2017	AF	29 PAF versus 32 persistent AF versus 35 permanent AF	Progressive deterioration of FMD observed from PAF ($7.96 \pm 1.22\%$) to persistent AF ($6.35 \pm 1.18\%$) to permanent AF ($4.81 \pm 1.15\%$) ($p = .001$). Inverse correlation between permanent AF and FMD ($r= -0.061$, 95% CI 0.032–0.081) even after adjustment for comorbid diseases
Siasos et al. [93]	2015	AF	65 (30 PAF and 35 Permanent AF)	Duration of AF inversely associated with FMD (rho$= -0.058$, $p=.006$). This was even after adjustment for confounders
Simons et al. [94]	1998	Hypercholesterolaemia	32	Median FMD improved compared to baseline with atorvastatin (2.2% $\rightarrow$ 5.5%) and simvastatin + cholestyramine therapy (1.8% $\rightarrow$ 4.5%) ($p<.01$ for both). FMD at baseline correlated with HDL cholesterol ($r = 0.49$, $p<.01$). Change in FMD was inversely correlated with baseline FMD ($r= -0.54$, $p<.001$)
Ulgen et al. [57]	2014	AF	40 PAF versus 40 controls	FMD in AF group was significantly lower relative to control group (5.27 versus 6.65, $p = .001$)
Woo et al. [95]	2002	Hyperhomocysteinemia	17	Folic acid supplementation significantly improved FMD compared to placebo ($7.4 \pm 2\%$ versus $8.9 \pm 1.5\%$, $p<.0001$)

FMD is expressed as the maximum percentage change in vessel diameter after cuff release relative to baseline vessel diameter; a low percentage suggesting poor endothelial function [100]. FMD responses can be affected by external factors such as sleep deprivation, hyperhomocysteinemia, caffeine, smoking, antioxidant therapy, menstrual cycle and time of day [75,101–106]. Thus it is important to control these factors to prevent bias.

Conclusion

The endothelium is vital in maintaining vascular haemostasis and its functional integrity is a fundamental element for vascular health. However, disruption in its role can lead to endothelial dysfunction. Endothelial dysfunction is present in patients with AF. These patients are generally older and have other co-morbidities such as hypertension, hypercholesterolaemia and diabetes, all of which exert adverse effects on the

endothelial function. Thus adding further complexity to the assessment of endothelial function and its management. Consequently, endothelial dysfunction in patients with AF is associated with poor outcomes.

Modulation of endothelial function is possible suggesting that endothelial dysfunction is a reversible condition as shown by several studies who have looked at FMD pre and post-intervention and shown improvement in FMD post-intervention [71,74,75,77,78,85,95,97]. FMD reflects dynamic vascular haemostasis and thus raises the possibility of adopting a treat-to-target approach, where FMD can be monitored intermittently with the goal of normalising of enhancing vascular health [13]. It is not yet known whether endothelial dysfunction is simply a biomarker of AF or an intermediate step in a causal pathway in developing AF, perhaps it is both. However, improved endothelial function is a clinical marker of atherogenic risk factor modification [107].

There are several non-invasive methods available to assess vascular function including FMD. Patients with AF should be considered for vascular function assessment and attempts made to modify their vascular function. These are at present limited to the traditional risk factor modifications such as exercise, weight reduction, smoking control, better diabetes control, antithrombotic and antihypertensive treatments.

Disclosure statement

ORCID

Ahsan A. Khan http://orcid.org/0000-0003-1617-1464
Graham N. Thomas http://orcid.org/0000-0002-2777-1847
Gregory Y. H. Lip http://orcid.org/0000-0002-7566-1626

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