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REVIEW

Is reversal of endothelial dysfunction still an attractive target in modern cardiology?

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Abstract

Although the endothelium has a number of important functions, the term endothelial dysfunction is commonly used to describe impairment in its vasodilatory capacity. There have been numerous studies evaluating the relationship between endothelial dysfunction and cardiovascular disease, however assessment of endothelial function is perhaps still primarily thought of as a research tool and has not reached widespread clinical acceptance. In this review we explore the relationship between endothelial dysfunction and cardiovascular disease, its prognostic significance, methods of pharmacological reversal of endothelial dysfunction, and ask the question, is reversal of endothelial dysfunction still an attractive target in modern cardiology?

Key words: Endothelium; Vascular; Nitric oxide; Atherosclerosis; Risk factors; Flow-mediated dilatation

Core tip: There is an abundance of evidence suggesting that endothelial dysfunction is present throughout a wide spectrum of cardiovascular disease and is an independent indicator of adverse prognosis. Despite this, perhaps due to lack of standardisation of investigative techniques, endothelial function assessment is not yet routinely undertaken, despite a number of therapies which have been shown to have beneficial effects on the endothelium. More studies are required to judge whether assessment of endothelial function can impact on clinical management and prognosis.

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INTRODUCTION

For many years the vascular endothelium was thought of as simply a selectively permeable barrier between the intra- and extravascular compartments. However, discovery by Furchgott *et al*[1] that the large blood vessels of mammals only dilate if the endothelium is intact due to its response to nitric oxide (NO) was the first step in our understanding that the endothelium is a key modulator of cardiovascular health. Indeed, the integrity of the vascular endothelium is essential for providing adequate blood flow and antithrombotic activity. While these are key functions of the endothelium, in the context of cardiovascular health, the key function of the endothelium is maintenance of vasodilatation in response to NO. The healthy human endothelium maintains a vasodilated state as a baseline, in part due to NO production from L-arginine by nitric oxide synthase. NO then diffuses into the endothelium, leading to increased cyclic guanosine monophosphate (GMP) production and vasodilatation[2]. Damage to the endothelium, whether anatomical or functional can cause a disturbance of this pathway leading to endothelial dysfunction. There are three potential mecha-

nisms that can lead to endothelial dysfunction (either in isolation or combination): reduced production of NO[3]; reduced availability of NO[4] or antagonism of NO by endothelium derived contracting factors[5]. Indeed, although NO is the main endothelium-derived relaxing factor there are other factors active on the endothelium, all of which play a key role in its health. Other endothelium-derived relaxing factors include prostacyclin and endothelium-derived hyperpolarizing factor, both of which can show increased activity in response to a decrease in NO. Meanwhile, there are several endothelium-derived contracting factors causing vasoconstriction such as endothelin-1, thromboxane A_2 and prostaglandin H_2. Nevertheless, the majority of clinical studies have concentrated on NO, and this will be the focus of our review.

NO has a number of vascular protective roles including inhibition of platelet aggregation and leucocyte adhesion, however endothelial dysfunction can be simply described as the imbalance of vasodilatation and vasoconstriction caused by vasoactive substances acting on the endothelial cells[6]. Endothelial dysfunction is present in a number of cardiovascular conditions such as diabetes, hypercholesterolemia and hypertension and seems to be an important feature in the pathogenesis of the atherosclerotic disease process.

In this review, we will discuss the association of endothelial dysfunction with the cardiovascular disease, its prognostic relevance, methods for reversing endothelial dysfunction and their impact on outcome.

HOW DO WE QUANTIFY ENDOTHELIAL FUNCTION CLINICALLY?

Theoretically endothelial function can be measured in any artery. In most methods the endogenous NO-dependent vasodilation is measured using a pharmacological agonist such as acetylcholine (Ach) or other substances which stimulate endogenous NO production. Comparison is then made with NO-independent vasodilatation using substances such as glyceryl trinitrate. Invasive measurement of the coronary artery response to acetylcholine is a validated measurement of coronary artery endothelial function and was the first method used to demonstrate endothelial function[7,8]. Using quantitative coronary angiography the change in diameter of the artery can be measured in response to Ach. In dysfunctional coronary arteries Ach causes reduced vasodilatation or apparently paradoxical vasoconstriction due to the unopposed direct smooth muscle muscarinic action of Ach at apparently high concentrations[9].

Non-invasive measures include what is considered by many as gold standard, venous occlusion plethysmography. This technique is used to assess forearm blood flow (in the brachial artery) in response to an inflated blood pressure cuff. The inflation of the cuff occludes venous return (but not arterial inflow) thus creating a "reservoir" of blood within the anatomically isolated limb region (forearm). The rate of vessel swelling can be measured as a surrogate for vascular resistance while the volume increases in proportionally in relation to the forearm blood flow[10]. Endothelial function, which is closely related to NO bioactivity, can be measured by constructing dose-response curves to escalating doses of Ach and measuring the rate of change in arm swelling by strain gauge. One advantage of this technique is that measurement of forearm blood flow in the contralateral arm can be used as a further within patient control, allowing optimal reproducibility[11]. Nevertheless, the requirement for arterial cannulation may limit patient tolerability and repeatability.

Flow-mediated dilation (FMD) is probably the most common method of endothelial function assessment. This technique involves using ultrasound to measure the peripheral arterial response (again, usually the brachial artery) to temporary ischemia caused by inflation and release of a cuff. Release of the cuff causes an increase in blood flow and therefore shear stress which stimulates NO release and leads to vasodilatation. The increase in diameter of the blood vessel from baseline can be measured by two dimensional ultrasound and is related (but not exclusive) to NO bioavailability, giving an excellent measure of endothelial function which can again be compared to dilatation using endothelium-independent vasoactive substances[12]. Of note, FMD has been shown to have excellent correlation with coronary endothelial function[13].

A more recently developed method of assessment is peripheral arterial tonometry (PAT). This technique allows non-invasive measurement of vasomotor function by measuring plethysmographic changes in the fingertip pulse. Again, the endothelium-dependent response can be ascertained by arterial cuff occlusion[14]. PAT has also been shown to correlate well with both coronary endothelial function and FMD[15,16].

WHAT IS THE CLINICAL RELEVANCE OF ENDOTHELIAL DYSFUNCTION?

While several methods have been developed to assess endothelial function in different arterial beds, there can only be any benefit to quantification of endothelial dysfunction if there is evidence that it can be used to identify groups with an adverse prognosis.

Several studies have shown a relationship between endothelial dysfunction, coronary disease risk factors and atherosclerosis. One of the earliest studies revealing this relationship was carried out by Ludmer *et al*[8] who discovered that in patients with both mild and advanced coronary artery disease (CAD) there was paradoxical vasoconstriction induced by acetylcholine. Evidence of endothelial dysfunction has also been noted in patients with risk factors for CAD but without angiographically significant CAD, suggesting that endothelial dysfunction may indeed predate the development of clinically significant atherosclerosis[17,18]. Age[19], diabetes mellitus[20-22], smoking (both active and passive)[23-25], hypertension[26] and hyperlipidemia[27,28] have all been associated with endothelial

dysfunction prior to the development of clinically significant CAD. Furthermore, patients with a combination of risk factors (such as smoking and hypercholesterolemia) have been shown to have worse endothelial function than those with a single risk factor[29].

The presence of endothelial dysfunction has been shown to be a predictor of cardiovascular events independent of the arterial bed studied or method of assessment[30,31]. Much of this effect is due to the fact that endothelial dysfunction is invariably present whenever there is end-organ damage. This is clinically manifested as atherosclerosis, left ventricular hypertrophy, small vessel brain ischemia and renal impairment, leading to significant morbidity and mortality[32-34]. Not unreasonably, endothelial function assessment could be considered as the barometer of vascular health[35]. Large studies investigating the prognostic value of endothelial function assessment using FMD are summarized in Table 1.

So why has endothelial dysfunction assessment not been adopted more widely clinically? As we have discussed, FMD appears to be the most robust and widely used technique, yet it very rarely appears in any clinical guidelines. One reason may be that although FMD does have predictive value, there are of course several other risk factors that may be easier to assess which are also predictors of adverse cardiac outcome[31]. Secondly, although many studies have reported the excellent reproducibility and variability of FMD measurement in multiple institutions[36-39], these studies all rely on following an "ideal" protocol for obtaining FMD measurements. According to a recent paper published by the European Society of Cardiology, this includes 10 min rest for the patient prior to measurement, correct cuff placement, an occlusion time of 5 min and measurement 45-60 s after cuff release[40]. Clearly, following this prescribed methodology takes some time and is prohibitive to its use within the clinical setting, however, not using these techniques can lead to inaccurate measurements, thus diluting the utility of FMD measurements. Automated analysis software may well overcome some of the difficulties regarding standardization of results[37], however, when it is much simpler to check a cholesterol level or measure a blood pressure, it is easy to see why FMD has perhaps not yet penetrated the clinical realm. Also, FMD is strongly influenced by baseline brachial artery diameter, and changes in FMD tend to vary based on this[41]. Finally, the absence of normal values makes it difficult to provide any clinically relevant recommendations to non-experts in the field of endothelial function assessment.

ENDOTHELIAL DYSFUNCTION IN ASYMPTOMATIC PATIENTS

In asymptomatic patients, most clinicians use the assessment of risk factors, such as the Framingham Risk score, to assess cardiovascular risk[42]. Studies looking at the independent prognostic value of FMD in prediction of adverse events in asymptomatic patients have shown mixed results. Suzuki *et al*[43], in the Northern Manhattan Study, evaluated 819 patients with cardiovascular risk factors and showed that patients with metabolic syndrome and endothelial dysfunction (measured by FMD) were at a higher risk for stroke, myocardial infarction MI or cardiovascular death than those without endothelial dysfunction. In one of the largest studies to date, Yeboah *et al*[44] reported that in 2792 patients with 5 years of follow up, FMD was an independent predictor of a poor outcome, however it did not appear to add much to the overall predictive model. Further large cohort studies have also shown that FMD is an independent predictor of adverse events, although there is some question as to whether the small incremental increase in prediction provided by the assessment of endothelial function mandates the routine clinical use of FMD[31,44-46]. Indeed, other large studies have not found incremental predictive value with use of FMD. A large study of 842 asymptomatic patients in the Northern Manhattan Study found that although FMD did predict adverse outcomes it was not an independent predictor when included in a multivariable analysis including traditional cardiac risk factors[47]. Two further studies found that while FMD was not an independent predictor of adverse events, several components of endothelial function measurement, such as hyperemic velocity and assessment of resistance artery endothelial function, were[48,49]. In general, there is still doubt that endothelial dysfunction is a predictor of adverse cardiovascular events in asymptomatic patients.

ENDOTHELIAL DYSFUNCTION IN ESTABLISHED CAD (CHRONIC STABLE CAD)

Endothelial dysfunction in the coronary arteries is closely related to systemic endothelial dysfunction[13]. In patients with CAD the presence of severe endothelial dysfunction has been shown to be a predictor of cardiac death, myocardial infarction or revascularization[50]. These results have been replicated in other large studies[51-53]. Endothelial dysfunction has also been related to adverse plaque characteristics (such as lipid-rich necrotic cores) in this group of patients[54,55]. FMD has also been shown to be an independent predictor of in-stent restenosis in patients with single vessel coronary artery disease undergoing percutaneous coronary intervention[56]. Elsewhere in the vascular tree, FMD has also been shown to be a predictor of post-operative MACE in patients with hypertension[57], early peripheral arterial disease[58] and those undergoing vascular surgery[59].

ENDOTHELIAL DYSFUNCTION IN ACUTE CORONARY SYNDROMES

Over the past decade there has been an increasing realization that acute coronary syndromes (ACS) cannot be predicted simply by risk factors or even the presence of ob-

Table 1 Large studies evaluating the prognostic value of flow-mediated dilation

Ref.	Number of patients	Cohort	Asymptomatic Patients?	Length of follow-up (mo)	Outcome	Result	Independent value of FMD?
Rossi *et al*[45]	2264	Post-menopausal women	Yes	45 ± 13	CV death, MI, revascularisation, TIA, stroke	FMD was a predictor of MACE independently of traditional cardiac risk factors.	Yes
Patti *et al*[56]	136	Patients with single-vessel coronary artery disease undergoing PCI	No	6	In-stent restenosis	Patients with impaired FMD were more likely to suffer in-stent restenosis.	Yes
Gokce *et al*[59]	187	Patients undergoing vascular surgery	No	1	CV death, MI, unstable angina, ventricular fibrillation, stroke, raised troponin	FMD was an independent predictor of MACE in the immediate post-operative period.	Yes
Brevetti *et al*[58]	139	Patients with peripheral arterial disease	No	23 ± 10	CV death, MI, revascularisation, TIA, critical limb ischaemia	FMD was an independent predictor of events over the follow-up period.	Yes
Chan *et al*[53]	152	Patients with coronary artery disease	No	34 ± 10	CV death, MI, revascularisation, claudication	FMD was a strong independent predictor of risk even accounting for carotid plaque burden.	Yes
Shimbo *et al*[47]	842	Asymptomatic multi-ethnic cohort	Yes	36	Vascular death, MI, stroke	FMD was able to predict adverse events but not independently.	No
Suzuki *et al*[43]	819	Asymptomatic multi-ethnic cohort including patients with metabolic syndrome	Yes	81 ± 21	Vascular death, MI, stroke	Patients with the combination of metabolic syndrome and endothelial dysfunction had a significantly worse outcome.	No
Yeboah *et al*[44]	2792	Mixed cohort of patients > 65 yr	No	60	CVD death, MI, stroke, congestive heart failure, claudication, revascularisation	FMD was an independent predictor of risk but added little to traditional risk stratification.	Yes
Muiesan *et al*[57]	172	Hypertensive patients	No	95 ± 37	CV death, MI, revascularisation, arrhythmia, TIA, critical limb ischaemia, retinal artery occlusion	FMD below median was independently associated with adverse outcome.	Yes
Shechter *et al*[46]	618	Healthy subjects (mixed)	Yes	55.2 ± 21.6	CV death, MI, stroke, congestive revascularisation	FMD predicted adverse outcome independently.	Yes
Katz *et al*[77]	259	Heart failure patients (LVEF < 40% and NYHA class 2-3)	No	28	Death or cardiac transplantation	FMD is associated with increased adverse outcome in ischaemic and non-ischaemic heart failure.	Yes

PCI: Percutaneous coronary intervention; MACE: Adverse major cardiovascular events; MI: Myocardial infarction; TIA: Transient ischaemic attack; FMD: Flow-mediated dilation.

structive CAD[60,61]. The development of the "vulnerable plaque" concept that leads to ACS (and sudden cardiac death) is influenced by omnipresent endothelial dysfunction *via* several methods. Endothelial dysfunction leads to reduced expression of anti-inflammatory mediators, leading to plaque destabilization[62]. In particular, Endothelin-1, a potent vasoconstrictor, is released significantly more by the dysfunctional endothelium as well as directly at the site of unstable coronary plaque lesions[63]. The predominant vasoconstriction of the dysfunction coronary artery may cause plaque rupture directly[64]. Finally, the dysfunctional endothelium also has reduced antithrombotic tendency allowing thrombus formation[65].

Endothelial dysfunction is also a predictor of adverse outcome in patients after ACS. Improvement of endothelial function post-ACS is associated with improved prognosis[66,67]. Endothelial dysfunction has also been shown to lead to adverse remodeling post-ACS[68].

ENDOTHELIAL DYSFUNCTION IN HEART FAILURE

There is ample evidence to suggest that endothelial function is impaired in patients with both acute and chronic heart failure[69]. NO has been shown to be involved in myocardial relaxation[70], and reduction in NO availability (for the same reasons as seen in the vasculature) can impair left ventricular relaxation, causing diastolic dysfunction. The presence of diastolic dysfunction is associated with impaired FMD in patients with established CAD[71]. The presence of endothelial dysfunction has also been associated with perfusion defects and reduced coronary

flow in patients with suspected coronary artery disease thus potentially leading to impaired ventricular function[72,73]. In chronic heart failure there may be a vicious circle effect, by which the reduction of cardiac output leads to a decrease in vascular shear stress and NO production, therefore causing further worsening of endothelial function[74]. FMD has also been shown to be a predictor of adverse outcome in heart failure patients[75-78].

In acute heart failure, there is also a reduction in NO availability leading to vasoconstriction and increased vascular stiffness, increasing afterload. There is also increased endothelin-1 production and oxidative stress, again placing further strain on the heart and vasculature[79,80]. Coronary artery endothelial dysfunction has been shown to predict progression of allograft vasculopathy and mortality in patients with orthoptic heart transplantation[81,82].

Endothelial dysfunction is associated with adverse outcome in patients with LV dysfunction[83-85]. It has also been shown to be a good predictor of response to cardiac resynchronization therapy (CRT)[86].

CAN ENDOTHELIAL DYSFUNCTION BE REVERSED?

We have shown that there is substantial evidence to support the role of endothelial dysfunction in the development and progression of cardiovascular disease and its prognostic role. Because of this there has been a significant interest in finding methods to ameliorate endothelial dysfunction. Despite many drug classes being evaluated, only a few have shown concrete benefits on the endothelium. Large clinical studies evaluating pharmacological endothelial dysfunction reversal are summarized in Table 2.

Some of the most studied drug classes are those that act on the renin-angiotensin system, namely angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-Ⅱ receptor antagonists (ARBs). These drugs have several anti-oxidant and anti-inflammatory effects, reducing superoxide (thus reducing oxidative stress) and endothelin-1 activity[87]. Angiotensin Ⅱ stimulates angiotensin type 1 receptors (AT1) to mediate arteriolar vasoconstriction and remodelling, superoxide anion production, renal sodium reabsorption, aldosterone secretion and endothelin-1 release[88]. Many of these actions affect the vascular endothelium adversely. On the other hand stimulation of the angiotensin type 2 (AT2) receptor by angiotensin has mainly opposing actions to those of AT1 stimulation and recently has been shown to contribute to endothelial NO release[89]. AT2 production can be reduced by angiotensin converting enzyme inhibitors which also increase both tissue and plasma bradykinin by inhibiting kininase II[90]. By stimulating the B2 receptors, bradykinin mediates the release of NO, prostacyclin and the endothelial hyperpolarizing factor; agents that produce vasodilation[91-93]. The large TREND study provided evidence that quinapril was able to reverse endothelial dysfunction[94]. The beneficial effects of ACEIs have been replicated by several other studies[95-98]. Angiotensin-Ⅱ receptor antagonists have also shown similar results[99,100].

Spironolactone and eplerenone, which have mineralocorticoid receptor antagonist activity have received much attention recently. They have been reported to improve NO bioactivity in patients with heart failure[101]. The mechanism(s) by which aldosterone impairs endothelial function is unclear. Aldosterone enhances vascular responsiveness to pressor agents such as norepinephrine and angiotensin Ⅱ[102]. Also, aldosterone can cause direct vascular smooth muscle contraction *via* a non-genomic pathway that has not yet been characterised. Both drugs have however been shown to improve endothelial function in patients with heart failure and hypertension[103-106].

Beta-blockers and diuretics have generally been shown to have no effect on endothelial function however, newer beta-blockers such as nebivolol and carvedilol have shown some beneficial effects on reversal of endothelial dysfunction[107-109]. Nebivolol has a direct effect on NO synthase while carvedilol has some antioxidant properties. Calcium channel antagonists also improve endothelial dysfunction by several pathways, particularly in the coronary microvasculature by indirectly increasing in intracellular smooth muscle cell cGMP, which is the second messenger of NO and mediates vasodilation[110,111]. Two additional mechanisms have been described to explain the effects of calcium channel blocker in the forearm circulation. The first explanation is that most calcium channel blockers have antioxidant activities, reducing production of superoxide anions[88,89]. The second explanation involves a reduction in endothelin-1 release by calcium channel blockers. Endothelin-1 is a potent vasoconstrictor and it is released from the endothelium[112]. Normally, there is a balance between vasoconstrictive and vasodilating substances in the vasculature but in hypertension, the bioavailability of endothelin might be increased in parallel with a reduction in NO bioactivity. It has shown that calcium channel blockers improved NO bioactivity by reducing endothelin release[100,101]. In addition, Cardillo *et al*[113] have recently shown that in patients with essential hypertension, the increased endothelin activity is partly responsible for the increased vascular tone. Hence, in a model where vasoconstrictive activity is increased, such as hypertension, a reduction of endothelin release would improve NO bioactivity. CCBs may also improve other aspects of endothelial dysfunction, reducing tissue plasminogen activator activity, thus reducing thrombogenic risk by decreasing platelet activation[114].

Statins also have proven beneficial effects on endothelial dysfunction in addition to their effects on lipids[115-118]. Reduction in LDL-cholesterol is thought to be the main method by which statins improve endothelial function, however, they also enhance expression and activity of NO synthase and reduce C-reactive protein (which has deleterious effects on the endothelium)[119,120]. On a similar, intriguing, theme of non-antihypertensive therapies improving endothelial function, recent studies have also suggested that drugs such as metformin[121], ranolazine[122] and allopurinol[123] may also improve endothelial function.

Table 2 Selected studies examining pharmacological reversal of endothelial dysfunction

Ref.	Drug	Cohort	Design	Results
Mancini *et al*[94]	Quinapril	105 normotensive patients with coronary artery disease	Randomised double-blind, placebo controlled	Quinapril improved endothelial function compared to placebo as measured by coronary artery diameter response to acetylcholine
Higashi *et al*[96]	Various ACE inhibitors, beta-blockers, calcium channel blockers and diuretics	296 hypertensive patients	Multi-centre cohort study	ACE inhibitors significantly improved endothelial dependent vasodilatation compared to other drug classes as measured by forearm blood flow
Wassmann *et al*[97]	Candesartan, felodipine	47 patients with high cholesterol	Randomised double-blind, placebo controlled	Candesartan improved forearm blood flow compared to felodipine or placebo
Ghiadoni *et al*[98]	Nifedipine, amlodipine Perindopril, telmisartan, atenolol, nebivolol	168 patients with hypertension	Randomized, single-blind, parallel-group	Only perindopril improved FMD (although perindopril, telmisartan, nifedipine and amlodipine reduced oxidative stress and increased plasma antioxidant capacity)
Tzemos *et al*[99]	Valsartan, amlodipine	25 hypertensive patients	Randomised double-blind, crossover	Valsartan improved forearm blood flow
Takagi *et al*[100]	Telmisartan	Mixed; 398 patients	Meta-analysis of 7 studies	Statistically significant increase in FMD by 48.7%
Farquaharson *et al*[101]	Spironolactone	10 patients with NYHA class I-II heart failure	Randomised, double-blind placebo-controlled crossover study	Spironolactone improved forearm blood flow compared to placebo
MacDonald *et al*[103]	Spironolactone	43 patients with NYHA class I-II heart failure	Randomised, double-blind crossover study	Spironolactone improved forearm blood flow compared to placebo
Abiose *et al*[104]	Spironolactone	20 patients with NYHA class III-IV congestive heart failure	Cohort study	Spironolactone improved FMD at 4 wk with a sustained improvement at 8 wk
Tzemos *et al*[107]	Nebivolol, atenolol	12 hypertensive patients	Randomised, double-blind crossover study	Only nebivolol was able to improve endothelial dependent vasodilation
Pasini *et al*[108]	Nebivolol, atenolol	40 hypertensive patients with 40 controls	Randomised double-blind parallel group	FMD improved only in the group treated with nebivolol
Matsuda *et al*[109]	Carvedilol	29 patients with coronary artery disease	Randomised, placebo controlled	Carvedilol significantly improved FMD after 4 mo treatment
Agewall *et al*[116]	Atorvastatin	20 healthy smokers, 20 healthy non-smokers	Open label placebo controlled randomised cross-over	Smokers had a lower baseline FMD. Atorvastatin improved FMD in smokers but had no effect in non-smokers
Ostad *et al*[117]	Atorvastatin, ezetimibe	58 patients with coronary artery disease	Double-blind, randomised, parallel group	High-dose atorvastatin improved FMD significantly more than low dose atorvastatin + ezetimibe independently of improvement in LDL cholesterol
Gounari *et al*[118]	Rosuvastatin, ezetimibe	Patients with heart failure	Double-blind, placebo controlled, cross-over trial	Rosuvastatin caused a significant improvement of FMD compared to ezetimibe and independent of LDL cholesterol and baseline brachial artery diameter
Pitocco *et al*[121]	Metformin	42 type 1 diabetics without overt cardiovascular disease	Randomised double-blind, placebo controlled	Significant improvement in FMD by 1.32% compared to placebo
Lamendola *et al*[122]	Ranolazine	30 type 2 (non-insulin dependent) diabetics without overt cardiovascular disease	Randomised double-blind, placebo controlled	Significant improvement in FMD compared to placebo after 2 wk of ranolazine therapy
Kao *et al*[123]	Allopurinol	67 patients with CKD stage 3 and LV hypertrophy	Randomized, double-blind, parallel-group	Significant improvement in FMD compared to placebo after 9 mo of allopurinol therapy

FMD: Flow-mediated dilation.

DOES REVERSAL OF ENDOTHELIAL DYSFUNCTION HAVE ANY PROGNOSTIC IMPACT?

Given that several classes of drugs do seem to lead to an improvement in endothelial function, the next step is to consider whether these effects are translated into a prognostic benefit. There are however only a few studies which address this issue. Modena *et al*[124] evaluated 400 post-menopausal women with hypertension and endothelial dysfunction in an attempt to assess whether

an improvement in FMD using antihypertensive drugs would predict a better prognosis. The authors found that improvement in endothelial function after 6 mo of therapy was associated with a much reduced event rate (6% *vs* 21.3% in those patients with persistently impaired endothelial dysfunction). One problem might perhaps be the fact that therapeutic options which improve endothelial function also have other beneficial effects on the cardiovascular system independent of their vasodilatory contribution. A recent study in patients with heart failure showed that patients in whom endothelial function improved following institution of optimal medical therapy had a much better prognosis than those in whom there was no improvement (hazard ratio 3.0 for those with persistently impaired endothelial function)[78].

Furthermore, confounding effects of medications also need to be considered-for example, hormone replacement therapy with estrogens in post-menopausal women does cause vasodilatation, however this beneficial effect is negated by their pro-thrombotic tendency. Another potential role for identification of endothelial dysfunction is that of screening. Given that there is abundant evidence to suggest that endothelial dysfunction is present before the development of clinically significant cardiovascular disease it might be beneficial to identify patients at potential risk of future events and offer disease modifying therapy. Again however this question has not yet been answered.

While numerous drugs that improve endothelial dysfunction have been shown to improve mortality, very few studies have specifically looked at the beneficial prognostic effects of endothelial dysfunction. This is presumably because when designing studies investigating these drugs it is very difficult to isolate the effect of endothelial dysfunction reversal given the multi-site action of drugs such as ACE inhibitors and statins. Of course, as the beneficial effects of these drugs are now well established, trials specifically looking at the prognostic benefit of endothelial dysfunction are perhaps less of a priority.

CONCLUSION

In this review we have demonstrated the methods of endothelial function assessment, the significance of endothelial dysfunction (particularly as a precursor) to cardiovascular disease and its prognostic significance. Several aspects need further exploration. First, despite the widespread use of FMD in clinical trials, is it the best way of assessing endothelial dysfunction? Certainly, the failure of the technique to obtain widespread use in a clinical setting despite many years of use in clinical trials and a reasonable amount of prognostic evidence behind it would suggest that it may never be adopted in the cardiology community. However, the failing of FMD seems to be more due to technical issues (such as the time taken to measure it and operator variability) rather than a disbelief in its results or the importance of endothelial function. The development of PAT and interest in other aspects of endothelial function such as circulating biomarkers relating to thrombosis and inflammation may prove to be easier methods of assessing endothelial function. If an easier method could be found then (presuming it showed similar prognostic value as FMD in large-scale studies) perhaps this would have more widespread clinical applicability. Indeed, in our unit, FMD is only used in research studies and is not used at all clinically. The standardization of the method is of key importance with regards to whether FMD can truly penetrate the clinical arena. Secondly, should endothelial dysfunction be used as an end-point to guide therapy or should it be simply thought of as another risk factor? And if so, are there any other potential therapies which might independently modulate endothelial function? Finally, does improving endothelial function lead to improved clinical outcomes in both primary and secondary prevention?

In summary, and in answer to the question posed by the title of this review, there is evidence to suggest that reversal of endothelial dysfunction might still be a target which might improve cardiovascular outcomes in the modern era, however, we do not yet have convincing evidence that it does as yet. We know that reversal is possible, but whether it is beneficial in identifying a higher risk group in primary prevention (in addition to traditional risk factors) or as a target in secondary prevention remains a question with an as yet elusive answer. It may be that FMD (and other measures of endothelial dysfunction) is more of a marker of overall cardiovascular health (predicting adverse outcome similarly to biomarkers such as B-type natriuretic peptide and troponin), rather than a therapeutic target itself. Nevertheless, there is ample evidence that therapies that improve cardiovascular outcome (by various pathways), also seem to improve endothelial function. Given the prognostic value of FMD, it would seem logical that at least some of these beneficial effects may be mediated by an improvement in endothelial function. However, as long the most validated measurement of endothelial function (FMD) cannot reach widespread use clinically, it will remain difficult to promote the idea that reversal of endothelial dysfunction should be a primary target of treatment in its own right. Indeed, to answer the question posed in the title of this review, we believe that while reversal of endothelial dysfunction is an attractive target in modern cardiology, we still require further studies to ascertain whether directly targeting reversal of endothelial dysfunction is a worthwhile target in modern cardiology.

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