Introduction

The aim of this review is to provide a summary of the current knowledge on endothelial dysfunction, particularly focused on its clinical implications in coronary artery disease (CAD). Both coronary and peripheral endothelial dysfunction will be discussed, as peripheral endothelial function often serves as a surrogate for coronary vascular function.

The vascular endothelium is a monolayer of cells covering the internal lumen of all blood vessels, thereby separating the blood from the vascular wall and organ tissues. The vascular endothelium serves different functions: (i) it is an anti-coagulant surface; (ii) it regulates fluid and molecule traffic between blood and tissues; (iii) it contributes to the vascular homeostasis and repair; and (iv) it plays a crucial role in vascular tone and blood flow regulation.

Cardiovascular risk factors produce endothelial dysfunction by various complex mechanisms, among which oxidative stress is considered an important agent. Increased intracellular superoxide produces endothelial dysfunction by several mechanisms such as NO inactivation and formation of peroxynitrite, NO synthase uncoupling, prostacyclin formation inhibition, endothelin expression stimulation, and a reduced NO signalling due to inhibition of soluble guanylate cyclase activity. All these mechanisms are combined to promote a vasoconstrictive and pro-coagulant milieu in endothelial dysfunction.

When endothelial function is altered, any of its functions could be impaired. Yet, for practical reasons, it is the current standard to measure endothelial function by the study of its vasomotor regulation function. It is also customary to use the generic term ‘endothelial function’ as a synecdoche for endothelium-dependent vascular reactivity.

Since myocardial oxygen extraction is very high at basal conditions, any additional metabolic demands must be met by an increase in myocardial blood supply. In normal conditions, the coronary circulation is capable of increasing its basal flow by at least three times. This maximal increase in coronary blood flow is known as coronary flow reserve (CFR). The main agent in this blood flow regulation is the coronary endothelium, which produces vasodilator substances such as nitric oxide (NO) and prostacyclin and vasoconstrictor substances, mainly endothelin-1, in response to different physiological stimuli. Endothelial shear stress caused by arterial blood flow, and autacoids such as acetylcholine, histamine, and bradykinin are the main physiological triggers for endothelium release of NO, which in turn produces a guanylyl-cyclase-mediated relaxation of vascular smooth muscle (Figure 1).

However, important, the vascular endothelium is not the only determinant of coronary blood flow. Coronary microvascular function can also be impaired due to other mechanisms as thrombi, debris embolization, ventricular hypertrophy, myocardial, and vascular
oedema, smooth muscle dysfunction, etc. When microvascular function is impaired by an endothelium-independent factor, CFR is reduced, limiting the overall vasodilator capacity. Endothelium-independent microvascular dysfunction has been shown as a predictor of adverse cardiovascular events in diverse settings from early atherosclerosis to post-stenting and acute myocardial infarction. Thus, although the focus of this article is set on the prognostic importance of endothelial dysfunction, it has to be acknowledged that microvascular endothelium-independent dysfunction can also be an important source of flow dysregulation and adverse clinical outcomes.

Assessment of endothelial function

There are several ways to measure endothelial function in the clinical setting. Although it is far beyond the scope of this review to discuss the methodology in detail, we will very briefly summarize the most common possibilities. For further reading, we refer to recent comprehensive reviews. All the techniques have in common that they measure the response of the vessels to endothelial-dependent stimuli, mainly reactive hyperaemia (shear stress) or vasoactive substances.

The coronary vasomotion can be assessed directly and invasively by coronary angiography. In principle, intracoronary vasoactive stimuli, mainly acetylcholine, are infused to trigger an endothelium-dependent vascular reaction. A functioning endothelium releases NO in response to acetylcholine, causing vasodilation in the epicardial arteries and the coronary microcirculation. Epicardial vasodilation is measured by quantitative angiography or intravascular ultrasound (IVUS); vasodilation in the microcirculation is assessed measuring the coronary blood flow with a Doppler wire, since the microcirculation is the main determinant of coronary resistance, and therefore of coronary blood flow. If the coronary endothelium is dysfunctional, NO release is deficient, and paradoxical vasoconstriction, due to direct muscarinic smooth muscle stimulation, is observed in the epicardial arteries or the microcirculation. Non-endothelial vasodilation can be measured using other drugs, such as adenosine or nitroprusside for the microcirculation, and nitroglycerine or nitroprusside for the epicardial arteries. Other non-pharmacological approaches which have been described for coronary endothelium-dependent vasodilation assessment are based on flow-mediated dilation (FMD) in response to hyperaemia, like exercise, mental stress or pacing, or on sympathetic nervous system activation, like the cold pressor test.

The same principle of FMD can also be applied to the peripheral vasculature. Briefly, ultrasound images of the brachial artery are used to determine arterial diameter before and after reactive hyperaemia-induced vasodilation. Reactive hyperaemia is achieved by causing limb ischaemia with a blood pressure cuff for a few minutes. Flow-mediated dilation is commonly expressed as percent change in artery diameter. This technique correlates with invasively measured epicardial coronary function and has been widely used in clinical research.

Peripheral arterial tonometry (PAT) is a newer technique based on the change in finger pulse wave amplitude in response to reactive

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Figure 1: Endothelium-derived vasoactive substances. Shear stress and activation of a variety of receptors leads to a release of nitric oxide by inducing endothelial nitric oxide synthase. It exerts relaxation of vascular smooth muscle cells and exerts antiproliferative effects as well as inhibits thrombocyte aggregation and leucocyte adhesion. Other endothelium-derived relaxing factors, including endothelium-derived hyperpolarizing factor and prostacyclin, are also shown. ACE, angiotensin-converting enzyme; Ach, acetylcholine; AI, angiotensin I; All, angiotensin II; AT1, angiotensin 1 receptor; Bk, bradykinin; COX, cyclooxygenase; ECE, ET-converting enzyme; EDHF, endothelium-derived hyperpolarizing factor; ETA and ETB, endothelin A and B receptors; ET-1, endothelin-1; L-Arg, L-arginine; M, muscarinic acetylcholine receptor; PGH2, prostaglandin H2; ROS, reactive oxygen species; S1, serotoninergic receptor; TX, thromboxane receptor; TXA2, thromboxane; 5-HT, serotonin. Reproduced with kind permission from Springer Science and Business Media. Source: Springer. Pflügers Arch. Eur J Physiol (2010) 459:1005–1013. Human endothelial dysfunction: EDRFs. Flammer and Lüscher.
Endothelial dysfunction in early asymptomatic atherosclerosis

The development of atherosclerosis is a continuous process starting already early in life and has a long asymptomatic initial phase and a slow progression caused and accelerated by the presence of different risk factors. Importantly, endothelial dysfunction is one of the first recognizable signs of its development and is present long before the sometimes-devastating consequences of atherosclerosis appear. Endothelial dysfunction has been reported in relation with most, if not all, risk factors for atherosclerosis, such as hypertension, diabetes, hyperlipidaemia, and ageing. Endothelial dysfunction not only is a marker of atherosclerosis but it itself contributes to the progression of atherosclerosis by various mechanisms, by promoting coagulation, vasoconstriction, and deficient or pathological vascular repair. Interestingly, endothelial dysfunction itself can cause myocardial ischaemia even in the absence of relevant coronary stenosis. Thus, it has been proposed that endothelial dysfunction constitutes a first stage of atherosclerosis, summarizing the influence of all cardiovascular risk factors, and can itself be the cause of cardiovascular events. As endothelial function is associated with risk factors, the absence of endothelial dysfunction might depict a particularly favourable state.

In primary prevention, physicians mainly rely on classical risk scores (e.g. Framingham or SCORE) to assess the risk for patients. The measurement of endothelial function, however, as it depicts the overall burden of risk and includes so far unknown factors, might be a better measure for re-classification and personalized decision-making.

For example, Li et al. recently showed a worse endothelial function, as measured by PAT, in patients with the metabolic syndrome compared with those without it, even though both had the same number of classical risk factors present. Interestingly, the Northern Manhattan Study prospectively followed 819 subjects during a mean of 81 months for cardiovascular events, focusing on the incremental predictive value of FMD and its relation to metabolic syndrome. Patients with metabolic syndrome had a higher rate of events (HR: 1.5), but patients with metabolic syndrome and endothelial dysfunction had the highest rate (HR: 2.6), which shows an incremental prognostic value of endothelial dysfunction. In type 2 diabetes a normal peripheral endothelium-dependent vasodilation (as established by an FMD >8%) has an excellent negative predictive value for CAD.

The cardiovascular Health Study evaluated the relation between brachial FMD and cardiovascular events in a cohort of 2700 elderly patients without known cardiovascular disease. Over a 5-year follow-up period, FMD was a predictor of cardiovascular events, even after adjustment for other risk factors. More recently, the multi-ethnic study of atherosclerosis (MESA) study, by the same group, proved the prognostic value of FMD independently of the Framingham Risk Score in over 3000 patients followed over 5 years. Similar results were obtained in a cohort of 2264 asymptomatic postmenopausal women followed up for a mean period of 45 months, in whom endothelial function was also evaluated by FMD. However, in other series, as the FATE study and the PIVUS study, FMD failed to add incremental prediction value or even correlate with events. However, in the FATE study hyperaemic velocity, a correlate of microvascular dilation, did correlate with events and it provided additional independent prognostic value. Methodological differences and a younger and presumably healthier population in the FATE study may be accountable for this disparity.

Thus, the presence of endothelial function may serve as an important tool to re-classify the risk of the patients beyond the conventional risk factors. Future studies thus have to better delineate which patients benefit most from a measurement and which method is best to assess endothelial dysfunction.

Endothelial dysfunction in symptomatic patients without obstructive coronary artery disease

Over 20% of the patients referred to a coronary angiogram due to chest pain do not present significant obstructive coronary stenosis. Yet, a considerable proportion of these patients suffer from typical angina, and often myocardial perfusion defects can be demonstrated. Many of these patients present an abnormal coronary endothelial function, which can result in chronic ischaemia and facilitate acute ischaemic events, as explained below.

A study in 27 patients showed how abnormal flow response to selective infusion of acetylcholine in the left anterior descending artery (LAD) in patients with angina and non-obstructive CAD was related to concordant exercise-induced myocardial perfusion defects on SPECT. Lerman demonstrated that the perfusion defect could be provoked at rest using the same method of selective LAD acetylcholine infusion. The results of these two studies show how coronary vascular dysfunction without severe obstructive disease can be the source of myocardial ischaemia due to endothelial dysfunction and the resulting flow dysregulation.

Because the vascular endothelium not only regulates vascular tone and flow, but has also important roles in vascular permeability and thrombosis homeostasis, endothelial dysfunction not only may lead to chronic stable myocardial ischaemia, but can also be the source of atherosclerosis progression and acute ischaemic events (Figures 2). One prospective study from the Mayo Clinic in 157 patients with mild CAD, and an invasive coronary endothelial function test by acetylcholine infusion in the LAD, showed coronary endothelial dysfunction to be an independent predictor of cardiovascular events. Schachinger et al. had similar results in another study with 147 patients, using the same method. In two other studies performed in diabetic patients without obstructive CAD, in whom coronary endothelial function was tested by the cold pressor test, coronary endothelial dysfunction showed a correlation with myocardial perfusion defects and long-term adverse cardiovascular events.
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<td>NOMAS39</td>
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<td>OR 2.89 for patients with endothelial dysfunction and metabolic syndrome; OR 1.64 (NS) for endothelial dysfunction alone.</td>
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<td>FMD</td>
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<td>MESA41</td>
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<td>3026</td>
<td>FMD</td>
<td>CV death, MI, angina, revascularization, cardiac arrest, stroke</td>
<td>OR 0.79 FMD/unit SD; 29% correct reclassification of risk.</td>
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<td>Rossi42</td>
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<td>Healthy, male, low-intermediate FRS</td>
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<td>Invasive brachial—FMD—radial tonometry</td>
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<td>Rubinstein10</td>
<td>Symptomatic; low risk stress tests or normal coronary angiogram</td>
<td>270</td>
<td>PAT</td>
<td>MACE + Revascularization + CV hospitalization</td>
<td>Events 48 vs. 28% at 7 years, P = 0.03</td>
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<td>Suwaidi17</td>
<td>Symptomatic: no significant coronary atherosclerosis</td>
<td>157</td>
<td>Direct coronary</td>
<td>MI + CV death + heart failure + revascularization</td>
<td>Only patients with severe endothelial dysfunction had events (14%)</td>
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<td>Schachinger47</td>
<td>Symptomatic: no stenosis or single vessel</td>
<td>147</td>
<td>Direct coronary</td>
<td>MI + CV death + heart failure + revascularization + angina + stroke + peripheral revascularization</td>
<td>Patients with events had significantly poorer vascular response to acetylcholine</td>
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<td>Symptomatic; with and without CAD</td>
<td>308 (132 with CAD; 176 without)</td>
<td>Direct coronary</td>
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<td>72 diabetics 56 controls</td>
<td>Direct coronary, cold pressor test</td>
<td>Sudden cardiac death, MI, angina, stroke, TIA, revascularization</td>
<td>Diabetics with abnormal cold pressor test showed higher MACE rates</td>
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**Table 1** Studies of cardiovascular events in patients with endothelial dysfunction and early or stable coronary artery disease
In symptomatic patients without obstructive CAD, non-invasive peripheral microvascular endothelial function measured by PAT is also able to discriminate subjects at high risk for adverse cardiovascular events.\(^{50}\)

**Endothelial dysfunction in stable coronary artery disease**

In patients with stable obstructive CAD, endothelial function is an independent predictor of symptoms and cardiovascular risk. In one study, 308 patients with and without CAD were studied by direct coronary endothelial function testing. Abnormal response to selective intracoronary acetylcholine infusion, both in the epicardial and microvascular circulation, was an independent predictor of MACE, even after adjusting for the presence of CAD.\(^{51}\) Another study in 281 patients with documented CAD showed that peripheral endothelial dysfunction also identifies subjects at a higher risk for cardiovascular events.\(^{52}\)

Diabetic patients constitute a high-risk population for symptomatic and silent myocardial ischaemia. Two substudies of the Detection of Ischemia in Asymptomatic Diabetics study evaluated the utility of FMD to predict silent myocardial ischaemia and microvascular damage as expressed by microalbuminuria.\(^{37}\) In these studies, a cutoff value of 8% FMD showed a high negative predictive value for silent myocardial ischaemia, and microalbuminuria correlated with abnormal endothelium-dependent vasoreactivity.

Although endothelial dysfunction is a systemic condition, and thus non-invasive functional tests correlate with invasive tests, endothelial dysfunction in the epicardial arteries can also be focal. One study showed a correlation between focal endothelial dysfunction and a larger necrotic core, as measured by IVUS.\(^{54}\) This study provides a rationale for endothelial dysfunction being related to acute coronary syndrome (ACS). Whether in this case endothelial dysfunction is the cause or the expression of a vulnerable plaque is uncertain.

**Endothelial dysfunction after coronary artery stenting**

Coronary stenting results in acute endothelial injury, sometimes even associated with arterial dissection or haematoma, and in the presence of prosthetic metallic material in the vessel lumen; in the case of drug-eluting stents (DES), this material is associated with an artificial polymer and a drug. A functional vascular endothelium prevents platelet adhesion, aggregation, and activation by the secretion of prostacyclin and NO, and maintains an adequate balance between pro-coagulant (tissue factor) and anti-coagulant (heparin, protein C/S) and thrombolytic factors (tissue plasminogen activator),\(^{33}\) an injured or dysfunctional endothelium loses its antiplatelet function and may favour pro-coagulant activity, which in combination with a reduced blood flow due to vasoconstriction can increase the risk of stent thrombosis.\(^{55}\)

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**Figure 2** Illustration of the reciprocal interaction between endothelial dysfunction, inflammation and the natural history of coronary artery disease. Blue arrows marked with the box ‘ED’ represent processes in which endothelial dysfunction modifies the evolution or prognosis of coronary artery disease. Red arrows represent ways in which coronary artery disease contributes to a worse endothelial function.
Several studies with DES have shown a persistently abnormal endothelium-dependent vasoreactivity in coronary arteries after DES implantation (Figure 3). Both the sirolimus\textsuperscript{56,57} and the paclitaxel\textsuperscript{58} stents exhibit a detrimental effect extending over at least 6 months, while the second-generation zotarolimus stent seems to have a more benign albeit not neutral behaviour.\textsuperscript{59} In the study by Togni, endothelial response was evaluated by bicycle exercise, while in the rest of the studies the method used was acetylcholine infusion in the left coronary artery.

The new bioresorbable coronary scaffolds may be promising in their ability to allow long-term restoration of coronary vasomotion, especially at the stented segments. Data from the ABSORB stent\textsuperscript{60,61} (a polylactide bioresorbable everolimus-eluting scaffold) showed an abnormal response of the segment distal to the scaffold at 12 months, which improved significantly at 24 months; interestingly, the scaffolded segments showed improved endothelial-dependent and independent vasomotion at 24 months of implantation, which was related to scaffold degradation assessed by IVUS.

Lim et al. recently showed that in patients who were evaluated in the catheterization laboratory due to chest pain (in average 1 year after stent placement) coronary vascular function was not worse than in controls.\textsuperscript{62} Thus, although it is generally accepted that coronary endothelial dysfunction may be impaired in the short term, there might not be long-term relevance. Interestingly, however, endothelial dysfunction as assessed by brachial FMD has been reported as a predictor of in-stent restenosis.\textsuperscript{63}

**Endothelial dysfunction in acute coronary syndrome**

Most frequently, in ACS there is a local inflammatory status which affects endothelial function and can make atherosclerotic plaques more prone to rupture and platelet adhesion, vasospasm, and stasis, which can precipitate coronary thrombosis.\textsuperscript{64} Microvascular function is frequently impaired, but it is uncertain whether this is a contributor or a consequence of the ACS, and it may be to a large extent endothelial independent, due to thrombi and debris embolization, myocardial oedema, and other factors. Endothelial function testing is particularly challenging in ACS. The unpredictable nature of ACS onset, the unstable condition of the patient and the early dramatic impairment in microvascular function, make it very difficult to obtain and interpret data concerning vascular reactivity in this context.

Coronary endothelial dysfunction seems to be present in most patients with acute coronary syndrome, and is reversible in a matter of months.\textsuperscript{65} In patients with unstable angina, endothelium-dependent vasoreactivity parallels inflammatory activity as expressed by C-reactive protein levels.\textsuperscript{66}
Endothelial function after ACS, measured in the peripheral circulation, has been shown as an independent predictor of MACE, and subsequent normalization of endothelial function in these patients predicts a lower risk of events.\(^{57,68}\) In patients with ST elevation ACS treated with primary angioplasty, FMD improvement 6 months after the event also correlates with a lower end-diastolic left ventricular volume.\(^{69}\)

**Endothelial dysfunction and heart failure**

Diastolic function is most frequently impaired in CAD, as a result of hypertension, obesity or hypertrophy, but also due to a reduced NO bioavailability in the myocardium. Nitric oxide plays a role in myocardial as well as vascular relaxation,\(^{70}\) and there is animal evidence that reduced NO availability due to reactive oxygen species (ROS) and NOS uncoupling is a causal factor in the development of diastolic dysfunction.\(^{71}\) In humans with CAD a high prevalence of diastolic dysfunction has been found, which correlates with endothelial dysfunction as assessed by FMD.\(^{72}\) Myocardial damage in CAD is frequently not limited to diastolic function, but can lead to systolic dysfunction due to myocardial necrosis and adverse remodelling, and it has already been mentioned how endothelial dysfunction impairs cardiac remodelling after an acute myocardial infarction.\(^{69}\)

Independently of the initial mechanism for heart failure, endothelial dysfunction plays a major role in the progression of the disease and has an important impact on clinical outcomes.\(^{73–75}\) The reduced stroke volume produces a lower endothelial shear stress, which causes a dysregulation in NO synthase isoforms gene expression,\(^{76,77}\) eventually leading to a reduced NO bioavailability.\(^{78}\) Furthermore, there is an additional reduction in NO bioavailability caused by direct NO destruction by ROS, mainly driven by an increase in angiotensin II and aldosterone activity, and purine metabolism.\(^{79}\)

Both coronary and peripheral endothelial dysfunction have been found in ischaemic as well as non-ischaemic heart failure patients,\(^{80–82}\) although peripheral endothelial dysfunction, measured by brachial FMD, seems to be less important in non-ischaemic patients,\(^{83}\) suggesting an incremental role of atherosclerosis in ischaemic patients.

The impaired peripheral endothelium-dependent vasodilation in response to exercise may limit the oxygen supply to skeletal muscles and thus have a negative impact on functional class. Peripheral endothelial dysfunction in heart failure is related to a worse clinical outcome.\(^{73–75}\) Conversely, regular exercise training has proved capable of restoring peripheral endothelial vasomotor function in patients with heart failure,\(^{84,85}\) which is accompanied by a higher exercise capacity. Thus, the systemic endothelial dysfunction in heart failure underscores the systemic nature of the disease and may be used to assess the effectiveness of therapy and predict events.

Endothelial dysfunction in heart failure, measured by brachial FMD, has been shown to be a pre-procedural predictor of good response to cardiac resynchronization therapy (CRT) in one study. Also, endothelial dysfunction improvement after CRT correlated with functional improvement.\(^{86}\) Two other studies have shown that CRT improves endothelial dysfunction in heart failure, and that this improvement is related to an increase in cardiac output, thus probably shear-stress mediated.\(^{87,88}\) This may be one path by which CRT improves symptoms in heart failure.

**Endothelial function after heart transplant**

After heart transplant the coronary endothelium is replaced by a presumably healthier one, stroke volume increases and so does endothelial shear stress, one of the main inducers of NO formation. However, the restoration of endothelial function is not immediate or complete, probably due to the persistence of atherosclerosis risk factors, inflammation and the use of immunosuppressive drugs such as cyclosporine.

Indeed, a high prevalence of coronary endothelial dysfunction has been described early after heart transplant.\(^{89}\) Coronary endothelial dysfunction in early post-transplant patients has been correlated with a higher risk of developing cardiac allograft vasculopathy (CAV) as expressed by intimal thickening\(^{90}\) and clinical events.\(^{91}\) When allograft vasculopathy is evident, coronary endothelial dysfunction is the norm.\(^{89}\) Immunosuppression with cyclosporine contributes to the development of endothelial dysfunction in post-transplant patients through various mechanisms, such as a decreased synthesis of NO,\(^{92}\) increased levels of endothelin\(^{93}\) and increased production of ROS.\(^{94}\) Sirolimus seems to have a more benign effect on endothelial function than cyclosporine.\(^{95}\)

The evolution of peripheral endothelial function after heart transplant remains controversial. Although it has been reported to improve early after transplantation,\(^{96}\) other studies have not confirmed this observation,\(^{97,98}\) and indeed have found a high and persistent prevalence of peripheral endothelial dysfunction in the first year post-transplantation. Peripheral endothelial dysfunction limits the vasodilator response to exercise, correlates with functional capacity and may be the cause why heart transplant recipients often do not achieve a normal functional status.\(^{99}\) Also, it has been found to correlate with the risk of developing CAV in the first year.\(^{97}\)

**Conclusion**

The assessment of endothelial function provides us with the ability to obtain information on the functional significance of cardiovascular disease at the different stages of the disease. There is a growing body of evidence to suggest that mainly the non-invasive assessment may intergrade into our practice to enable us to classify the risk of the patients with CAD and assess the success of therapy.

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