

Impaired Endothelium-Mediated Vasodilation in Heart Failure: Clinical Evidence and the Potential for Therapy

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ABSTRACT

Numerous studies in the last decade have clearly shown an attenuated endothelium-dependent vasodilation in patients with chronic heart failure. This abnormality has been demonstrated in the peripheral, pulmonary, and coronary circulation in patients with both ischemic and nonischemic cardiomyopathy; its magnitude correlates with the severity of symptoms. Endothelial dysfunction in patients with cardiomyopathy and a relatively new onset of symptoms suggests that change in endothelial function occurs early in the course of the disease. In contrast to other circulatory beds, renal circulation has shown significant vasodilatory response to endothelial stimulation. The development of endothelial dysfunction may not be homogenous, and its magnitude may differ among circulatory systems. Although the clinical implications of the attenuated endothelium-dependent vasodilation in heart failure are not clear, this condition may lead to decreased organ perfusion, impaired exercise tolerance, and progression of disease. Many therapeutic interventions have resulted in improvement of endothelial function in patients with heart failure. Some of these interventions have also proven effective in enhancing exercise capacity, symptoms, and survival in patients with heart failure. This association suggests a therapeutic role for improvement of endothelial function in patients with chronic heart failure.

The role of the endothelium in the control of vascular function and structure has been established in the last 2 decades.¹ Endothelial cells exert an important vasoregulatory effect through the release of several relaxing substances, including nitric oxide (NO), prostacyclin, atrial natriuretic peptide, adrenomedullin, and endothelium-derived hyperpolarizing relaxing factor.² At the same time, the endothelium is also capable of producing vasoconstrictor prostanoids.^{3,4} In normal endothelium, vasodilatory factors dominate and allow an appropriate in-

crease in blood flow. Continuous synthesis and release of NO are the major determinants of the vasodilatory effect of the endothelium.⁵ A loss of bioactive endothelial NO by either reduced synthesis or increased oxidative inactivation seems to play a central role in the development of endothelial dysfunction.^{6,7} Normal endothelium can become dysfunctional in various vascular disorders, including heart failure. We review the clinical evidence for endothelial dysfunction in patients with heart failure and therapeutic interventions that may result in restoration of endothelial function in this population.

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Evidence for Impaired Endothelium-Mediated Vasodilation in Chronic Heart Failure

In the last decade, several studies investigating endothelial function have provided strong evidence for a role

of endothelial dysfunction of both large-conduit and small-resistance vessels in patients with heart failure. Endothelium-dependent vasodilation has been studied by various methods and has been reported to be reduced in various circulatory beds.⁸⁻¹⁸ Kubo et al⁸ measured forearm blood flow response mediated by resistance vessel dilatation to the intraarterial administration of metacholine in patients with chronic heart failure (CHF) and showed an attenuated response. Katz et al⁹ studied the effect of acetylcholine on femoral artery (conduit vessels) flow measured by the Doppler technique and also showed a marked attenuation in endothelium-mediated vasodilation. These findings of impaired vasodilation were not related to etiology of CHF and were found in patients with both ischemic and nonischemic cardiomyopathy. Ramsey et al¹⁴ measured conduit artery distensibility in patients with CHF caused by dilated cardiomyopathy. They evaluated common iliac artery pulse-wave velocity and brachial artery diameter and blood flow by high-resolution ultrasound and continuous-wave Doppler and found a decreased response to acetylcholine and reactive hyperemia, indicating decreased distensibility of peripheral, conduit arteries in patients with heart failure.

Impaired endothelium-dependent vasodilation has also been shown in the coronary circulation in patients with heart failure. Treasure et al¹⁵ studied the effect of acetylcholine infusion into the left anterior descending coronary artery in 8 patients with heart failure caused by idiopathic dilated cardiomyopathy. Control patients had an increased coronary blood flow during acetylcholine infusion ($232\% \pm 40\%$), but no significant change was noted in patients with cardiomyopathy ($41\% \pm 24\%$). Canetti et al¹⁶ reported similar findings in a larger group of patients with heart failure caused by nonischemic cardiomyopathy. Mathier et al¹⁷ extended these observations to patients with new-onset idiopathic dilated cardiomyopathy and showed coronary endothelial dysfunction at both microvascular and epicardial levels early in the course of the disease.

Vasodilatory capacity of the pulmonary arterial vasculature in response to endothelial stimulation has recently been studied by Elkayam et al.¹⁸ Despite a comparable reduction in pulmonary resistance with adenosine in patients with and without CHF, the response to endothelial stimulation with acetylcholine was markedly attenuated in patients with heart failure.

The same group of investigators also studied the renal vasodilatory effect of endothelial stimulation in patients with CHF.¹⁹ Effects of intrarenal artery infusion of acetylcholine on the main renal artery diameter (conduit vessel) measured by intravascular ultrasonography and renal artery flow (resistance vessels) measured by intravascular Doppler technique were established. The study showed a significant change in renal artery diameter with

approximately 160% increase in renal blood flow as a response to endothelial stimulation with acetylcholine. The strong endothelial response suggests that unlike other circulatory beds, there is a preserved endothelial function in the renal circulation in patients with CHF. Renal endothelial stimulation may be a therapeutic target for enhancement of renal blood flow in patients with heart failure.

Impaired Endothelium-Dependent Vascular Relaxation as a Therapeutic Target in Heart Failure

A loss of bioactive endothelial nitric acid oxide NO is central to the development of endothelial dysfunction and is caused by either a reduced NO synthesis, increased oxidative NO inactivation by reactive oxygen intermediate, or both.⁷ Because of the evidence for increased oxygen free radicals in patients with CHF^{20,21} and previous studies showing improvement of NO-mediated vasodilation with antioxidants,²² Hornig et al²³ investigated the effect of vitamin C on flow-dependent arterial dilation in patients with CHF by high-resolution ultrasound and Doppler techniques to measure radial artery diameter and blood flow. They studied the vascular effect of short- and long-term vitamin C treatment at rest and during reactive hyperemia. Vitamin C restored flow-derived arterial dilatation mediated by NO after both short-term intraarterial administration and long-term (4 weeks) oral therapy. The results of this study support the concept that endothelial dysfunction in patients with CHF is at least partly related to accelerated degradation of NO by radicals and suggest a role for antioxidants in the long-term treatment of patients with heart failure.

Several investigations have attempted to improve endothelial dysfunction by increasing NO synthesis.⁷ Hornig et al²⁴ showed improvement of flow-dependent dilation of the conduit, radial artery with intraarterial infusion of the angiotensin-converting enzyme (ACE) inhibitor quinaprilat in patients with moderate heart failure (New York Heart Association class III). The same investigators showed that the mechanism for quinaprilat-mediated improvement of endothelial function is related to a decrease in bradykinin degradation.^{25,26} Because ACE is structurally identical to kinase II, an enzyme that inactivates bradykinin, ACE inhibition is also associated with decreased degradation of bradykinin and thus results in increased bradykinin-mediated endothelial production of NO,²⁷ prostacyclin,²⁸ and endothelium-derived hyperpolarizing factor.^{29,30} In contrast to the effect of quinaprilat, enalaprilat administration in this

study was not associated with a similar improvement in NO-dependent vasodilation of conduit arteries.²⁴ Nakamura et al³¹ studied the effect of low-dose enalaprilat infusion into the forearm vascular bed in normal individuals and patients with heart failure. Enalaprilat infusion was associated with improvement of the response of the forearm microcirculation to acetylcholine in control subjects and patients with mild CHF but not in patients with severe heart failure. The effect of enalaprilat on resistance blood vessels in the study by Nakamura et al³¹ was reduced by acetylsalicylic acid, whereas *N*^G-monomethyl-L-arginine failed to block the augmentation of flow. This study suggested therefore that potentiation of endothelium-dependent vasodilation induced by ACE inhibition is caused by bradykinin-dependent modulation of prostaglandin metabolism.³² Hornig et al²⁴ and Nakamura et al³¹ showed a different effect of enalaprilat on conduit vessels and peripheral resistance vessels. Failure of enalaprilat to affect conduit vessels may therefore not exclude a beneficial effect on peripheral resistance vessels.

NO is synthesized in endothelial cells from L-arginine by an endothelium-specific isoform of NO synthase. The semiessential amino acid L-arginine is converted to L-citrullin and in the process produces stoichiometric amounts of NO.^{7,33} Providing supplemental L-arginine to patients with inadequate NO has been suggested as a rational approach to increase NO production by the endothelium.⁷ Short-term infusion of L-arginine in patients with abnormal endothelium-dependent vasodilation caused by atherosclerosis or heart transplantation resulted in significant improvement in endothelial function. Hirooka et al³⁴ measured forearm blood flow by strain-gauge plethysmography in 20 patients with heart failure and showed attenuated acetylcholine-induced vasodilation. L-Arginine given by intravenous infusion significantly augmented acetylcholine-mediated vasodilation and decreased forearm vascular resistance during reactive hyperemia. Oral administration of L-arginine hydrochloride (5.6–12.6 g/d) for 6 weeks to a group of patients with heart failure reduced circulating levels of endothelin, increased forearm blood flow during forearm exercise, improved quality of life, and prolonged distances during a 6-minute walk test.³⁵ These results suggest a relationship between improvement in endothelium-dependent vasodilatory capacity and exercise capacity as well as quality of life in patients with heart failure.

NO induces vasorelaxation by increasing production of the second messenger cyclic guanosine monophosphate (cGMP), which activates soluble guanylate cyclase in the vascular smooth muscle. Identification of NO as a product of the normal endothelium with smooth muscle-relaxing effects has also led to the recognition that organic nitrates work by providing an exogenous source

of NO to the diseased blood vessel and, as such, may be used as a replacement therapy for the ailing vasculature.⁷ Many studies support this theoretical concept. Schwartz et al³⁶ showed that regional administration of a low, nonvasodilating dose of nitroglycerin (NTG) enhanced acetylcholine-induced, endothelium-dependent peripheral vasodilation in patients with CHF. Similarly, Elkayam et al³⁷ showed that an intracoronary infusion of a small, nonvasodilating dose of NTG prevented acetylcholine-mediated reduction in coronary artery diameter, indicating NTG-mediated restoration of normal endothelial response to acetylcholine. These results are in contrast to recently published data showing that continuous treatment with NTG leads to enhanced acetylcholine-induced vasoconstriction of large coronary arteries in patients with atherosclerosis and blunted peripheral vasodilator response to acetylcholine in healthy individuals.³⁸ The results by Schwartz et al³⁶ and Elkayam et al³⁷ suggest, however, that unlike in healthy individuals or patients without heart failure, stimulation of endogenous NO release by exogenous NO donors in patients with heart failure leads to improvement in endothelial function. We recently showed marked improvement in treadmill exercise time in patients with CHF already treated with ACE inhibitors after a 2-month treatment with high-dose organic nitrates.³⁹ Improvement of endothelial function may be at least partially responsible for nitrate-mediated change in exercise tolerance in patients with CHF. The concept of improvement of endothelial function via drug-induced augmentation of cGMP in the vascular smooth muscle is also supported by Katz et al⁴⁰ who showed an improvement in the vasodilatory response of the brachial artery after administration of sildenafil, a specific inhibitor of type 5 phosphodiesterase, the predominant isoenzyme for cGMP degradation in vascular smooth muscle.

Recently spironolactone in addition to standard therapy improved morbidity and mortality in patients with moderate-to-severe CHF.⁴¹ Several mechanisms may be responsible for this beneficial effect,⁴² including prevention of potassium and magnesium depletion, decreased sympathetic activity, and myocardial fibrosis. An unfavorable vascular effect of aldosterone was recently suggested by Ikeda et al⁴³ who showed in a tissue culture study that aldosterone mediated inhibition of NO release. Farguharson et al⁴⁴ studied the effect of spironolactone, a specific aldosterone antagonist, in patients with CHF and showed a significant increase in forearm blood flow response to acetylcholine with an associated increase in vasoconstriction caused by L-N-monomethyl-arginine. This study suggests an increase in NO bioactivity and improvement of endothelial function with spironolactone and provides an additional potential mechanism for the morbidity and mortality benefits with this drug in patients with CHF.

Short-term dobutamine treatment produced a sustained clinical effect in some patients with severely symptomatic CHF.⁴⁵ The persistence of dobutamine's clinical effect has been attributed to a sustained improvement in myocardial contractility and hemodynamic profile and to a training-like effect on the skeletal muscles.^{46,47} Patel et al⁴⁸ evaluated flow-mediated brachial artery vasodilation in response to peak reactive hyperemia in the forearm of 9 patients with severe CHF who were treated with dobutamine for 72 hours. Dobutamine increased brachial artery diameter during peak hyperemic response during the infusion, and the effect persisted for ≥ 2 weeks after discontinuation of the drug. This study suggested a persistent improvement of endothelium-mediated vasodilation after dobutamine administration. Potential mechanisms for dobutamine-mediated improvement in endothelial function provided by the investigators included an increased NO release because of increased blood flow and vascular shear stress^{49,50} and enhanced constitutive NO synthase gene expression.

Several studies show a favorable effect of physical training on endothelium-dependent vasodilation in animal models and patients with heart failure.⁵¹⁻⁵³ Hornig et al⁵⁴ studied the effect of physical training on endothelial function in patients with CHF and showed restoration of impaired flow-dependent dilation of the brachial artery after 4 weeks of daily handgrip training. In particular, the portion of flow-dependent dilation mediated by NO was significantly greater after physical training. Katz et al⁵⁵ showed significant enhancement of the vasodilatory response as manifested by increased forearm blood flow in response to brachial arterial administration of acetylcholine after 8 weeks of daily handgrip exercise in 12 patients with CHF. Hornig et al⁵⁴ and Katz et al⁵⁵ provide strong clinical evidence for a significant improvement in endothelium-dependent vasodilation in both the conduit as well as resistance vessels mediated by physical activity in patients with CHF.

Summary and Conclusions

Many studies in the last decade show an attenuated endothelium-dependent vasodilation in patients with CHF. This abnormality has been shown in the peripheral, pulmonary, and coronary circulations in patients with ischemic and nonischemic cardiomyopathy, and its magnitude correlates with the severity of symptoms. Endothelial dysfunction in patients with cardiomyopathy and new-onset symptoms suggests that change of endothelial function occurs early in the course of this condition. Relative responsiveness of the renal circulation to endothelial stimulation suggests that the development of

endothelial dysfunction is not homogenous and its magnitude differs among different organs.

Although the attenuated-endothelium dependent vasodilation in heart failure has been clearly established, more information is needed to establish the association of this phenomenon to clinical characteristics of heart failure, including decreased organ perfusion, impaired exercise tolerance, and progression of disease caused by vascular and ventricular remodeling. Improvement of endothelial function with a number of therapeutic interventions that have also proven effective in improving exercise tolerance, symptoms, and survival in patients with heart failure suggests a potential therapeutic role for enhancement of endothelial function in patients with CHF.

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