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Exercise-Induced Vasodilation in Forearm Circulation of Normal Subjects and Patients With Congestive Heart Failure: Role of Endothelium-Derived Nitric Oxide

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Objectives. **This study was undertaken to investigate the role of endothelium-derived nitric oxide in the regulation of forearm blood flow during exercise in normal subjects and patients with congestive heart failure.**

Background. **Nitric oxide–mediated vasodilation in response to muscarinic stimulation is impaired in the peripheral circulation of patients with congestive heart failure. Whether nitric oxide–mediated vasodilation during exercise is also impaired in patients with congestive heart failure is unknown.**

Methods. **Forearm blood flows (ml/min per 100 ml) were determined during rhythmic hand grip exercise at 15%, 30% and 45% of maximal voluntary contraction by venous occlusion plethysmography before and after regional inhibition of nitric oxide synthesis with administration of L-N^G-monomethylarginine (L-NMMA) in the brachial artery of 17 patients with congestive heart failure (mean age 49 years, mean left ventricular ejection fraction 0.22) and 10 age-matched normal subjects.**

Results. **Before administration of L-NMMA in the brachial artery, forearm blood flows in patients with congestive heart failure during rhythmic hand grip exercise at 15%, 30% and 45% of maximal voluntary contraction were slightly but not significantly lower than that of normal subjects ([mean ± SE] 6.8 ± 1.0, 8.5 ± 1.0 and 12.9 ± 1.7 ml/min per 100 ml, respectively, in patients with congestive heart failure vs. 6.6 ± 1.2, 11.6 ± 1.9 and 16.2 ± 1.9 ml/min per 100 ml, respectively, in normal subjects, p = NS). After administration of L-NMMA in the brachial artery, forearm blood flows in normal subjects significantly decreased by 10% to 21% during hand grip exercise but did not change during exercise in patients with congestive heart failure.**

Conclusions. **Regional inhibition of nitric oxide synthase with administration of L-NMMA in the brachial artery significantly decreased forearm blood flows during rhythmic hand grip exercise in normal subjects but not in patients with congestive heart failure. These findings suggest that nitric oxide–mediated vasodilation during submaximal exercise is impaired in the forearm circulation of patients with congestive heart failure.**

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Vascular endothelial cells synthesize nitric oxide from L-arginine in response to a diverse array of hormonal, chemical and physical stimuli (1,2). Nitric oxide is a potent vasodilating substance that appears to play an important role in modulating the vascular smooth muscle response to hormonal agonists and in regulating peripheral vasomotor tone at rest and during exercise in response to local changes in endothelial cell membrane shear stress produced by pulsatile blood flow (3,4).

In patients with congestive heart failure, agonist-induced nitric oxide–mediated vasodilation in response to muscarinic stimulation is impaired in the peripheral and coronary circulations (5–7). In contrast, there is evidence that basal release of nitric oxide may be normal or increased in patients with congestive heart failure compared with that in normal subjects (8–10). The role of nitric oxide in the regulation of peripheral vasomotor tone in response to exercise has not yet been characterized in patients with congestive heart failure.

Accordingly, the present study was undertaken to investigate nitric oxide–mediated vasodilation at rest and during exercise in normal subjects and patients with congestive heart failure. Forearm blood flow was determined with strain gauge venous occlusion plethysmography at rest and during rhythmic hand grip exercise before and after inhibition of nitric oxide synthesis with administration of a substituted arginine analog L-N^G-monomethylarginine (L-NMMA) in the brachial artery (11).

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Methods

Study patients. Sixteen men and one woman with chronic congestive heart failure participated in the study (mean age [±SD] 49 ± 11 years, range 32 to 65). The mean left ventricular ejection fraction determined by radionuclide angiography was 22%. The etiology of left ventricular dysfunction was idiopathic dilated cardiomyopathy in 14 patients, alcohol-related cardiomyopathy in 2 and adriamycin-related cardiomyopathy in 1. All patients had a history of symptomatic congestive heart failure and were clinically stable for at least 4 weeks before the study. Four patients were in New York Heart Association functional class I; 8 were in class II, and 5 were in class III. Cardiovascular medications, which included diuretic drugs, angiotensin converting-enzyme inhibitors and digoxin in all patients, were withheld for 24 h before the study. Patients with peripheral edema; serum sodium <136 mEq/liter; or history of diabetes mellitus, hypertension or hypercholesterolemia were excluded from the study.

Nine men and one woman without history of chronic medical illness participated as normal control subjects (mean age 43 ± 13 years, range 27 to 66, not statistically different from patients with congestive heart failure). The control subjects were nonsmokers, had normal results on the physical examination and were not taking medications. The study was approved by the ethical review board of the Columbia Presbyterian Medical Center. All patients and normal subjects gave written informed consent before the study.

Venous occlusion plethysmography. Forearm blood flow (ml/min per 100 ml of forearm volume) was determined with venous occlusion strain gauge plethysmography, as previously described in detail (12). Briefly, with the arm resting comfortably 10 cm above the right atrium, a mercury-in-Silastic strain gauge was placed around the widest portion of the upper third of the forearm. The strain gauge was electrically coupled to a plethysmograph (Parks Electronics) calibrated to measure percent change in volume. The plethysmographic tracings of forearm blood flow were digitally recorded on a personal computer at 40 Hz for later analysis (MacLab Software). For each measurement, forearm venous blood flow was occluded just proximal to the elbow with the rapid inflation of a blood pressure cuff to 40 mm Hg (Hokanson Instruments, model E 20). A wrist cuff was inflated to suprasystolic pressures 1 min before and during each measurement to exclude the hand circulation from the blood flow determination. The venous occluding cuff was inflated for 5 s at 15-s intervals; five plethysmographic measurements were averaged for determination of forearm blood flow at rest and during the last minute of each level of rhythmic hand grip exercise.

Rhythmic hand grip exercise protocol. Rhythmic hand grip exercise was performed according to the protocol previously reported by Longhurst et al. (13). Study subjects rhythmically squeezed a hand dynanometer in 15-s cycles that consisted of 5 s of steady hand grip pressure alternating with 10 s of rest. Three levels of exercise, corresponding to 15%, 30% and 45% of a previously determined maximal voluntary contraction were each performed for 3 min. Mean maximal voluntary contraction was similar in patients with congestive heart failure and normal subjects (15.5 ± 1.1 vs. 18.1 ± 1.5 psi, respectively, p = NS). Forearm blood flow was determined in the last minute of exercise during the 5-s period of each rest cycle immediately before the next hand grip contraction.

Drug preparation. L-N^G-Monomethylarginine (L-NMMA) (Sigma Chemical Co.), a competitive inhibitor of nitric oxide synthase, was prepared as a sterile, pyrogen-free solution in 5% dextrose in water and was administered as a continuous 1-ml/min infusion for 5 min at a dose of 4×10^{-5} mol/liter. This dose of L-NMMA has previously been demonstrated to be effective in inhibiting nitric synthase activity in isolated vascular tissue and in the intact human forearm circulation (11,14).

Study protocol. Subjects were studied in the postabsorptive state while resting in the supine position in a quiet, temperature-controlled room. To exclude the effects of prostaglandins on exercise-induced vasodilation, all subjects received 50 mg of indomethacin, a cyclooxygenase inhibitor, by mouth 1 h before the study (15). A 20-gauge angiocathetheter was placed in the brachial artery of the nondominant forearm under local anesthesia for regional drug administration. After brachial artery catheterization was completed, subjects rested for 1 h before measurements were made. Forearm blood flows were measured during supine rest and during rhythmic forearm hand grip exercise at 15%, 30% and 45% of maximal voluntary contraction. After completion of this sequence of forearm blood flow measurements, L-NMMA was administered into the brachial artery as a 5-min continuous infusion during supine rest. The sequence of forearm blood flow measurements at rest and during graded hand grip exercise was repeated immediately after completion of the intraarterial infusion of L-NMMA. Mean arterial pressure was recorded at 1-min intervals throughout the study with an automated cuff method (Critikon Inc.).

To determine the reproducibility of the measurements of forearm blood flow during exercise, rhythmic hand grip exercise at 15%, 30% and 45% was performed by an additional five normal subjects and five patients with congestive heart failure twice at a 30-min interval without other intervention. Forearm blood flow measurements during exercise were unchanged over time in both normal subjects and patients with congestive heart failure (Table 1).

Determination of peak oxygen uptake. To determine the relation of regional vascular responses to administration of L-NMMA with peak aerobic capacity, all but one patient with congestive heart failure performed a symptom-limited maximal exercise test on a motorized treadmill within 1 month of the forearm blood flow measurements. Peak oxygen uptake was determined by analysis of expired gases (SensorMedics) as the highest 20-s average value obtained in the last minute of exercise when the respiratory exchange ratio was >1.10.

Data analysis. All results are mean value ± SE. Forearm blood flows and mean arterial pressures in patients with congestive heart failure and normal subjects at rest, during exercise and during administration of acetylcholine and nitro-

Table 1. Reproducibility of Forearm Blood Flow Measurements at Rest and in Response to Hand Grip Exercise

	Forearm Blood Flow (ml/min per ml)			
	Normal Subjects (n = 5)		Patients With CHF (n = 5)	
	Baseline	30 min	Baseline	30 min
Rest	1.8 ± 0.2	2.0 ± 0.3	1.6 ± 0.3	1.7 ± 0.3
15% MVC	5.9 ± 0.9	5.5 ± 0.5	6.8 ± 0.9	6.6 ± 1.1
30% MVC	10.4 ± 1.7	10.2 ± 1.3	10.0 ± 2.0	11.0 ± 2.0
45% MVC	14.4 ± 2.6	14.0 ± 2.1	14.6 ± 2.2	14.0 ± 2.1

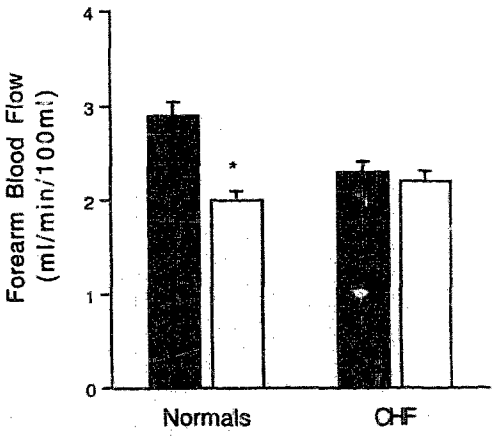
Data presented are mean value ± SE. CHF = congestive heart failure; MVC = maximal voluntary contraction.

glycerin were compared before and after administration of L-NMMA with a repeated measures analysis of variance model that consisted of one between-group factor (normal subjects vs. patients with heart failure) and two within-group factors (rest and three levels of exercise before and after administration of L-NMMA). Correlations between continuous variables of interest were analyzed with simple linear regression. A two-tailed probability value <0.05 was considered statistically significant.

Results

Effects of L-NMMA on rest forearm blood flow. Before administration of L-NMMA in the brachial artery, rest forearm blood flows were similar in normal subjects and in patients with congestive heart failure (2.8 ± 0.3 vs. 2.3 ± 0.3 ml/min per 100 ml, respectively). After administration of L-NMMA in the brachial artery, rest forearm blood flow significantly decreased by 25% in normal subjects but did not change in patients with congestive heart failure (Fig. 1).

Figure 1. Mean rest forearm blood flows in 10 normal subjects and 17 patients with congestive heart failure (CHF) before **(solid columns)** and after **(open columns)** administration of L-NMMA in the brachial artery. *p < 0.05 versus before L-NMMA.



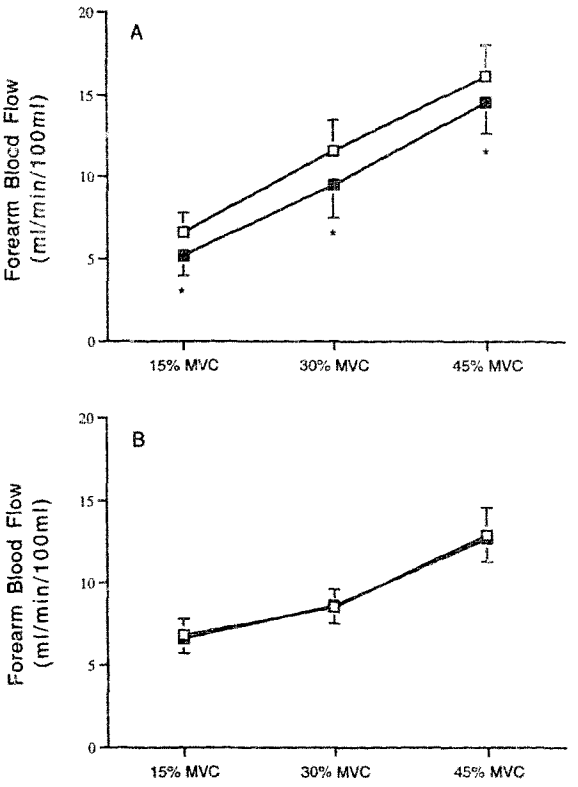


Figure 2. Mean forearm blood flows during rhythmic hand grip exercise at 15%, 30% and 45% of maximal voluntary contraction (MVC) in 10 normal subjects **(A)** and 17 patients with congestive heart failure **(B)** before **(open squares)** and after administration of L-NMMA in the brachial artery **(solid squares)**. *p < 0.05 versus before L-NMMA.

Effects of L-NMMA on forearm blood flow response to rhythmic hand grip exercise. Before administration of L-NMMA in the brachial artery, forearm blood flows in patients with congestive heart failure during rhythmic hand grip exercise at 15%, 30% and 45% of maximal voluntary contraction were slightly but not significantly lower than that in normal subjects (6.8 ± 1.0, 8.5 ± 1.0 and 12.9 ± 1.7 ml/min per 100 ml, respectively, in patients with congestive heart failure vs. 6.6 ± 1.2, 11.6 ± 1.9 and 16.2 ± 1.9 ml/min per 100 ml, respectively, in normal subjects, p = NS). After administration of L-NMMA in the brachial artery, forearm blood flows during rhythmic hand grip exercise significantly decreased in normal subjects at each level of exercise by 21%, 17% and 10%, respectively (all p < 0.05 vs. before L-NMMA values) (Fig. 2A) but did not change in patients with congestive heart failure (Fig. 2B).

Physiologic correlates of response to L-NMMA. In patients with congestive heart failure, the decrease in rest forearm blood flow in response to administration of L-NMMA was significantly correlated with both baseline rest forearm blood flow and peak oxygen uptake attained during treadmill exercise (r = 0.72 and 0.73, respectively, both p < 0.01) (Fig. 3).

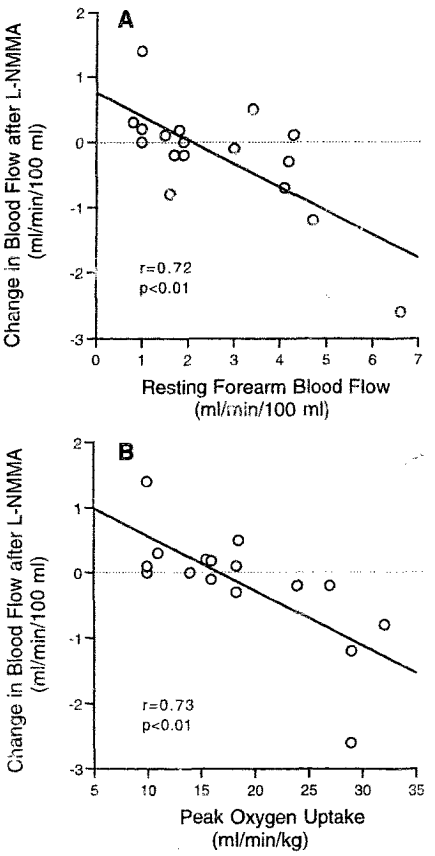


Figure 3. Changes in rest forearm blood flow in response to administration of L-NMMA as a function of initial rest forearm blood flow **(A)** and peak oxygen uptake **(B)**.

Effects of L-NMMA on mean arterial pressure. Before administration of L-NMMA in the brachial artery, mean arterial pressures at rest were similar in normal subjects and patients with congestive heart failure. During hand grip exercise, mean arterial pressure increased slightly in both normal subjects and patients with congestive heart failure. After administration of L-NMMA in the brachial artery, mean arterial pressures at rest and during hand grip exercise did not change in either normal subjects or patients with congestive heart failure (Table 2).

Discussion

The present data demonstrate that regional inhibition of nitric oxide synthase with administration of L-NMMA in the brachial artery significantly decreased forearm blood flows at rest and during rhythmic hand grip exercise in normal subjects but not in patients with congestive heart failure. These findings suggest that nitric oxide–mediated vasodilation at rest and during submaximal exercise is impaired in the forearm circulation of patients with congestive heart failure.

Effects of L-NMMA during exercise in normal subjects. Regional inhibition of nitric oxide synthase with L-NMMA decreased the forearm blood flows during rhythmic hand grip exercise by 10% to 21% in normal subjects. Previous studies of the effects of nitric oxide synthase inhibition with L-NMMA on exercise-induced hyperemia in normal subjects have yielded conflicting findings. Gilligan et al. (16) and Endo et al. (17) reported reductions in forearm blood flow during exercise in response to administration of L-NMMA in normal subjects that were comparable to those observed in the current study. In contrast, Wilson and Kapoor (18) reported no change in exercise hyperemia after administration of L-NMMA in normal subjects. The current findings provide evidence that the regional vasodilatory response during exercise is partly mediated by nitric oxide–dependent mechanisms. Increased shear stress at the endothelial cell lumen surface appears to be an important physiologic stimulus of endothelial nitric oxide synthesis during exercise. Shear stress at the endothelial cell surface has been demonstrated to be a potent stimulus of endothelial cell nitric oxide synthesis in endothelial cell culture and isolated vascular rings (19–22). In rats, systemic inhibition of nitric oxide synthase during exercise with the arginine analog N^G-L-arginine methyl ester (L-NAME) significantly reduced blood flow to muscles with a high percentage of oxidative fibers but did not change blood flow to muscles with a high percentage of glycolytic fibers (4). These findings suggest that nitric oxide contributes to the regulation of skeletal muscle blood flow as part of a coordinated system that preferentially supplies blood flow to oxidative muscles during submaximal exercise. These findings may account for the apparent attenuation of the effects of L-NMMA on forearm blood flow in normal subjects at the higher exercise work rates in the present study. At low work rates, when oxidative muscle fibers are selectively recruited, shear stress–induced nitric

Table 2. Effects of Administration of on Mean Arterial Pressure at Rest and During Rhythmic Hand Grip Exercise in 10 Normal Subjects and 17 Patients With Congestive Heart

	Mean Arterial Pressure (mm Hg)	
	Before L-NMMA (mean ± SE)	After L-NMMA (mean ± SE)
Rest		
Normal subjects	91 ± 4	89 ± 4
Pts with CHF	89 ± 4	87 ± 4
15% MVC		
Normal subjects	90 ± 5	92 ± 5
Pts with CHF	91 ± 4	90 ± 4*
30% MVC		
Normal subjects	91 ± 5	94 ± 4†
Pts with CHF	92 ± 4*	91 ± 4*
45% MVC		
Normal subjects	95 ± 5†	93 ± 4†
Pts with CHF	92 ± 4*	92 ± 4*

*$p < 0.05$ versus rest value in patients (Pts) with congestive heart failure (CHF). †$p < 0.05$ versus rest value in normal subjects. L-NMMA = L-N^G-monomethylarginine; MVC = maximal voluntary contraction.

oxide–mediated vasodilation may increase regional blood flow to oxidative fibers by augmenting mild local metabolic vasodilation mechanisms. At higher work rates, when a greater proportion of glycolytic muscle fibers are recruited, shear stress–induced nitric oxide–mediated vasodilation may contribute less to the overall vasodilation response as intense local metabolic vasodilation mechanisms are activated. The recent finding (23) that administration of L-NMMA does not alter peak hyperemic forearm blood flow after 10 min of arterial occlusion in normal subjects is consistent with this interpretation of the data.

Effects of L-NMMA during exercise in patients with heart failure. In contrast to normal subjects, regional inhibition of nitric oxide synthase with L-NMMA did not change blood flow during rhythmic hand grip exercise in patients with congestive heart failure. The current findings are in agreement with a previous study (24) of experimental heart failure in the rat, in which exercise-induced nitric oxide–mediated vasodilation in skeletal muscle circulation of the hind limb was significantly attenuated in rats with large myocardial infarction compared with that in rats with small myocardial infarction and sham-operated control rats. The current data also extend the findings of previous studies in patients with congestive heart failure that demonstrated decreased agonist-induced nitric oxide–mediated vasodilation in response to muscarinic stimulation in the forearm circulation of patients with congestive heart failure compared with that of normal subjects (5,6). Because the endothelium-dependent nitric oxide–mediated vasodilation during exercise may be induced by shear stress at the endothelial cell lumen surface, both shear stress–induced and agonist-induced endothelial nitric oxide production appear to be impaired in patients with congestive heart failure. Because shear stress and muscarinic receptor stimulation increase intracellular calcium and thereby regulate activity of nitric oxide synthase by different upstream signal transduction pathways (25), the current findings suggest that the mechanisms contributing to decreased nitric oxide–mediated vasodilation in patients with congestive heart failure may be related to downstream abnormalities in intracellular calcium homeostasis, altered regulation of the activity of nitric oxide synthase or increased degradation of nitric oxide. Forearm blood flows during rhythmic hand grip exercise in the patients with heart failure tended to be lower but were not significantly decreased compared with that in normal subjects. This finding is in agreement with previous studies that demonstrated that forearm blood flows in response to submaximal exercise and other metabolic vasodilating stimuli are reduced only in patients with severe heart failure (26–30). Since nitric oxide–mediated vasodilation during exercise was decreased in our patients, other compensatory vasodilatory mechanisms may have acted to maintain forearm blood flow during submaximal exercise in patients with congestive heart failure.

Effects of L-NMMA at rest. Administration of L-NMMA decreased rest forearm blood flow in normal subjects but not in patients with congestive heart failure in the current study. These findings are in accord with the majority of previous experimental studies that demonstrated impaired basal nitric oxide synthesis in isolated vascular rings and the intact circulation of animals with congestive heart failure compared with that in control animals (31–34). However, the current findings contrast two previous studies that demonstrated that administration of L-NMMA reduced rest blood flow in patients with congestive heart failure and normal subjects to a similar extent (8,9). The differences between the findings of these previous clinical studies and the current data may be related to differences in the severity of disease in the study cohorts. Both the current study and the previous report by Kubo et al. (9) demonstrated a significant correlation between the decrease in rest forearm blood flow in response to administration of L-NMMA and the basal rest forearm blood flow. The rest forearm blood flows in patients with heart failure in the current study cohort were somewhat lower than those reported by Kubo et al. (9). The decrease in rest forearm blood flow in response to administration of L-NMMA was also significantly correlated with peak oxygen uptake determined during treadmill exercise in the current study. This finding is in agreement with previous studies in animal models of congestive heart failure and in patients with congestive heart failure that demonstrated that abnormalities of endothelial-dependent vasodilation are most evident in advanced heart failure (24,34–36).

Limitations of the study. Interpretation of the findings of the current study is potentially confounded by the actions of vasoactive factors other than nitric oxide that contribute to the regulation of skeletal muscle blood flow during exercise (37). Inhibition of nitric oxide synthesis may increase formation of other vasodilating factors by decreasing blood flow to active muscle fibers and by direct effects on mitochondrial function that may alter local concentrations of vasodilatory metabolites in skeletal muscle (38). Because additional nitric oxide–independent vasodilatory mechanisms may have been recruited during inhibition of nitric oxide synthase, it is possible that the current findings underestimate the effects of nitric oxide in the regulation of exercise-induced hyperemia. Whether impaired exercise-induced nitric oxide synthesis contributes to reduced aerobic capacity during exercise of the lower extremities in patients with congestive heart failure cannot be determined from the present study. In normal human subjects, Leaf et al. (39) demonstrated that sustained exercise with the lower extremities was associated with increased metabolic activity of the L-arginine–nitric oxide pathway.

Conclusions. Regional inhibition of nitric oxide synthase with administration of L-NMMA in the brachial artery significantly decreased forearm blood flows at rest and during rhythmic hand grip exercise in normal subjects but not in patients with congestive heart failure. These findings suggest that endothelium-dependent nitric oxide–mediated vasodilation at rest and during submaximal exercise is impaired in the forearm circulation of patients with congestive heart failure.

References

1. Griffith TM, Lewis MJ, Newby AC, Henderson AH. Endothelium-derived relaxing factor. J Am Coll Cardiol 1988;12:797–806.
2. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med 1993;329:2002–12.
3. Sagach VF, Kindybalyuk AM, Kovalenko TN. Functional hyperemia of skeletal muscle: role of endothelium. J Cardiovasc Pharmacol 1992;20: S170–5.
4. Hirai T, Visneski MD, Kearns KJ, Zelis R, Musch TI. Effects of NO synthase inhibition on the muscular blood flow response to treadmill exercise in rats. J Appl Physiol 1994;77:1288–93.
5. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium-dependent vasodilation is attenuated in patients with heart failure. Circulation 1991;84:1589–96.
6. Katz SD, Biasucci L, Sabba C, et al. Impaired endothelium-mediated vasodilation in the peripheral vasculature of patients with congestive heart failure. J Am Coll Cardiol 1992;19:918–25.
7. Treasure CB, Vita JA, Cox DA, et al. Endothelium-dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. Circulation 1990;81:772–9.
8. Drexler H, Hayoz D, Munzel T, et al. Endothelial function in chronic congestive heart failure. Am J Cardiol 1992;69:1596–601.
9. Kubo SH, Rector TS, Bank AJ, et al. Lack of contribution of nitric oxide to basal vasomotor tone in heart failure. Am J Cardiol 1994;74:1133–6.
10. Winlaw DS, Smythe GA, Keogh AM, Schyvens CG, Spratt PM, Macdonald PS. Increased nitric oxide production in heart failure. Lancet 1994;344: 373–4.
11. Palmer RMJ, Rees DD, Ashton DS, Moncada S. L-Arginine is the physiological precrsor for the formation of nitric oxide in endothelium-dependent relaxation. Biochem Biophys Res Comm 1988;153:1251–6.
12. Greenfield ADM, Whitney RJ, Mowbray JF. Methods for the investigation of peripheral blood flow. Br Med Bull 1963;19:101–9.
13. Longhurst J, Capone RJ, Mason DT, Zelis R. Comparison of blood flow measured by plethysmograph and flowmeter during steady state forearm exercise. Circulation 1974;49:535–40.
14. Vallance P, Collier J, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. Lancet 1989;2:997–1000.
15. Nishimura H, Kubo S, Ueyama M, Kubota J, Kawamura K. Peripheral hemodynamic effects of captopril in patients with congestive heart failure. Am Heart J 1989;117:100–5.
16. Gilligan DM, Panza JA, Kilcoyne CM, Waclawiw MA, Casino PR, Quyyumi AA. Contribution of endothelium-derived nitric oxide to exercise-induced vasodilation. Circulation 1994;90:2853–8.
17. Endo T, Imaizumi T, Tagawa T, Shiramoto M, Ando S, Takeshita A. Role of nitric oxide in exercise-induced vasodilation of the forearm. Circulation 1994;90:2886–90.
18. Wilson JR, Kapoor S. Contribution of endothelium-derived relaxing factor to exercise-induced vasodilation in humans. J Appl Physiol 1993;75:2740–4.
19. Pohl U, Holtz J, Busse R, Bassenge E. Crucial role of endothelium in the vasodilator response to increased flow in vivo. Hypertension 1986;8:37–44.
20. Rubanyi GM, Romero JC, Vanhoutte PM. Flow-induced release of endothelium-derived relaxing factor. Am J Physiol 1986;250:H1145–9.
21. Cooke JP, Stamler J, Andon N, Davies PF, McKinley G, Loscalzo J. Flow stimulates endothelial cells to release a nitrovasodilator that is potentiated by reduced thiol. Am J Physiol 1990;259:H804–12.
22. Buga GM, Gold ME, Fukuto JM, Ignarro LJ. Shear stress-induced release of nitric oxide from endothelial cells grown on beads. Hypertension 1991;17: 187–93.
23. Tagama T, Imaizumi T, Endo T, Shiramoto M, Harasawa Y, Takeshita A. Role of nitric oxide in reactive hyperemia in human forearm vessels. Circulation 1994;90:2285–90.
24. Hirai T, Zelis R, Musch TI. Effects of nitric oxide synthase inhibition on the muscle blood flow response to exercise in rats with heart failure. Cardiovasc Res 1995;30:469–76.
25. Hutcheson IR, Griffith TM. Heterogenous populations of K^+ channels mediate EDRF release to flow but not agonists in rabbit aorta. Am J Physiol 1994;266:H590–6.
26. Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. J Clin Invest 1968;47:960–70.
27. Zelis R, Longhurst J, Capone RJ, Mason DT. A comparison of regional blood flow and oxygen utilization during dynamic forearm exercise in normal subjects and patients with congestive heart failure. Circulation 1974;50:137–43.
28. Jondeau G, Katz SD, Zohman LR, et al. Active skeletal muscle mass and cardiopulmonary reserve: Failure to attain peak aerobic capacity during maximal exercise in patients with congestive heart failure. Circulation 1992;86:1351–6.
29. Jondeau G, Katz SD, Toussaint JF, et al. Regional specificity of peak hyperemic response in patients with congestive heart failure: correlation with peak aerobic capacity. J Am Coll Cardiol 1993;22:1399–402.
30. Arnold AMO, Ribeiro JP, Colucci WS. Muscle blood flow during forearm exercise in patients with severe heart failure. Circulation 1990;82:465–72.
31. Ontkean M, Gay R, Greenberg B. Diminished endothelium-derived relaxing factor activity in an experimental model of chronic congestive heart failure. Circ Res 1991;69:1088–96.
32. Elsner D, Muntze A, Kromer EP, Riegger GAJ. Systemic vasoconstriction induced by inhibition of nitric oxide synthesis is attenuated in conscious dogs with heart failure. Cardiovasc Res 1991;25:438–40.
33. Teerlink JR, Gray GA, Clozel M, Clozel JP. Increased vascular responsiveness to norepinephrine in rats with heart failure is endothelium dependent: dissociation of basal and stimulated nitric oxide release. Circulation 1994; 89:393–401.
34. Wang J, Seyedi N, Xiao-Bin X, Wolin MS, Hintze TH. Defective endothelium-mediated control of coronary circulation in conscious dogs after heart failure. Am J Physiol 1994;266:H670–80.
35. Teerlink JR, Clozel M, Fischli W, Clozel JP. Temporal evolution of endothelial dysfunction in a rat model of chronic heart failure. J Am Coll Cardiol 1993;22:615–20.
36. Nakamura M, Ishikawa M, Funakoshi T, Hashimoto K, Chiba M, Hiramori K. Attenuated endothelium-dependent peripheral vasodilation and clinical characteristics in patients with chronic heart failure. Am Heart J 1994;128(Pt 1):1164–9.
37. Rowell LB. Human Cardiovascular Control. New York: Oxford University Press, 1993.
38. Shen W, Xiaobin X, Ochoa M, Zhao G, Wolin MS, Hintze TH. Role of nitric oxide in the regulation of oxygen consumption in concious dogs. Circ Res 1994;75:1086–95.
39. Leaf CD, Wishnok JS, Tannenbaum SR. L-Arginine is a precursor for nitrate biosynthesis in humans. Biochem Biophys Res Comm 1989;163:1032–7.